ARCHIVES

OF

INTERNAL MEDICINE

EDITORIAL BOARD

ARTHUR BLOOMFIELD, San Francisco
N. C. GILBERT, Chicago
REGINALD FITZ, Boston
J. H. MUSSER, New Orleans
RUSSELL M. WILDER, Rochester, Minn.

VOLUME 51
1933

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO

Medical
Mem

CONTENTS OF VOLUME 51

JANUARY, 1933. NUMBER 1

PAGE

Syndrome of Anemia, Glossitis and Dysphagia: Report of Eight Cases, with Special Reference to Observations at Autopsy in One Instance. M. M. Suzman, M.D., M.R.C.P., London, England 1

Blood Cholesterol in Thyroid Disease: I. Analysis of Findings in Toxic and in Nontoxic Goiter Before Treatment. Lewis M. Hurxthal, M.D., Boston 22

Intravenous Pressure: I. New Method of Determination. W. A. Brams, M.D.; L. N. Katz, M.D., and W. J. Schutz, M.D., Chicago 33

Transient Methemoglobinemia Due to Ammonium Nitrate. Leonard Tarr, M.D., New York 38

Endemic Nutritional Edema: II. Serum Proteins and Nitrogen Balance. John B. Youmans, M.D.; Austin Bell, M.D.; Dorothy Donley, M.D., and Helen Frank, A.B., Nashville, Tenn. 45

Detection of the Murmur of Acute Pericarditis: Description of a New Clinical Procedure. Harold N. Segall, M.D., Montreal, Canada 62

Acute Leukemia Following Lymphosarcoma. Katsuji Kato, Ph.D., M.D., and Alexander Brunschwig, M.D., Chicago 77

Toxicity of Purified Bile Preparations: III. Influence on Cardiovascular Responses. Fred A. Ries, M.D., and Eugene U. Still, Ph.D., Baltimore .. 90

Splenectomy in Sickle Cell Anemia: Report of a Case with Necropsy in an Adult on Whom Splenectomy Was Attempted. R. E. Ching, M.D., and L. W. Diggs, M.D., Memphis, Tenn. 100

Nourishment of the Myocardium Through Thebesian Vessels in a Heart in Which the Large Coronary Arteries and Veins Were Destroyed by Tuberculous Myocarditis. Samuel Bellet, M.D.; B. A. Gouley, M.D., and Thomas M. McMillan, M.D., Philadelphia 112

Treatment of Elderly Diabetic Patients with Cardiovascular Disease: Available Carbohydrate and the Blood Sugar Level. Samuel Soskin, M.D.; Louis N. Katz, M.D.; Solomon Strouse, M.D., and Samuel H. Rubinfeld, M.D., Chicago 122

Yellow Atrophy of the Liver: Report of a Case, with Particular Reference to the Metabolism of Copper. A. H. Gordon, M.D., and I. M. Rabinowitch, M.D., Montreal, Canada 143

Distention as a Factor in Intestinal Obstruction. Raymond C. Herrin, Ph.D., and Walter J. Meek, Ph.D., Madison, Wis. 152

Book Reviews 169

FEBRUARY, 1933. NUMBER 2

An Appreciation: William Sydney Thayer 173

Simmonds' Disease (Cachexia Hypophyseopriva): Report of a Case, with Postmortem Observations and a Review of the Literature. Solomon Silver, M.D., New York 175

Experimental Edema in Nephrectomized Dogs: II. The Rôle of Water and Chlorides. F. S. Barry, M.S.; A. L. Shafton, M.D., and A. C. Ivy, Ph.D., M.D., Chicago 200

Influence of the Pituitary Gland on Erythrocyte Formation. Robert C. Moehlig, M.D., and Gaylord S. Bates, M.D., Detroit 207

Infectious Polypoid Colitis. Ralph M. Larsen, M.D., Nashville, Tenn. 236

Tuberculosis of the Myocardium: Report of Six Cases, with Observations on Involvement of Coronary Arteries. B. A. Gouley, M.D.; Samuel Bellet, M.D., and Thomas M. McMillan, M.D., Philadelphia 244

FEBRUARY—Continued

PAGE

Paradoxical Breathing. Ephraim Korol, M.D., Lincoln, Neb. 264

Epinephrine: Its Effect on the Cardiac Mechanism in Experimental Hyperthyroidism and Hypothyroidism. Harold Rosenblum, M.D., San Francisco, and R. G. Hahn, M.D., and S. A. Levine, M.D., Boston 279

Syndrome of Pneumococcic Bronchial Obstruction: Experimental Production of Atelectasis or Lobar Pneumonia with Human Pneumonic Sputum; Suggestion for Preventive and Therapeutic Treatment. Pol N. Corylos, M.D., and George L. Birnbaum, M.D., New York 290

Book Reviews 324

MARCH, 1933. NUMBER 3

Cataphoretic Velocity of Streptococci as Isolated in Studies of Arthritis. Edward C. Rosenow, M.D., Rochester, Minn. 327

Bronchial Disinfection and Immunization: I. The Effects in Rabbits of Intrabronchial Injections of Various Chemical Disinfectants. John A. Kolmer, M.D., Philadelphia 346

Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery. Howard T. Karsner, M.D., Cleveland 367

Effect of Drugs on Cardiac Standstill Induced by Pressure on the Carotid Sinus. M. H. Nathanson, M.D., Minneapolis 387

Hyperplastic Sclerosis of the Pulmonary Artery and Arterioles: Report of a Case with Discussion of the Pathogenesis. Martin J. Sokoloff, M.D., and Harold L. Stewart, M.D., Philadelphia 403

Peptic Ulcers (Gastric, Pyloric and Duodenal): Occurrence in Guinea-Pigs Fed on a Diet Deficient in Vitamin C. David T. Smith, M.D., and M. McConkey, M.D., Ray Brook, N. Y. 413

Inherent Sensitivity of the Skin to Nickel and Cobalt (Allied Elements in Group VIII, Periodic System). Sloan G. Stewart, M.D., Philadelphia ... 427

Direct Comparison Between Specific and Nonspecific Serum Therapy for Type I Lobar Pneumonia. Wheelan D. Sutliff, M.D.; Maxwell Finland, M.D., and Thomas N. Hunnicutt, M.D., Boston 435

Nephritic Albuminuria. J. M. Hayman, Jr., M.D., and J. A. Bender, M.D., Cleveland 447

Spontaneous Subarachnoid Hemorrhage. A. L. Osterman, M.D., Wheeling, W. Va. 452

Oral Administration of Iron in Hypochromic Anemia. Clark W. Heath, M.D., Boston 459

Book Reviews 483

APRIL, 1933. NUMBER 4

"Dyspituitarism": Twenty Years Later, with Special Consideration of the Pituitary Adenomas. Harvey Cushing, M.D., Boston 487

Periduodenitis and Pericholecystitis: An Anatomic, Clinical and Roentgen Study of Adhesions in the Upper Right Quadrant. S. G. Meyers, M.D., and A. R. Bloom, M.D., Detroit 558

Acropachy: Secondary Subperiosteal New Bone Formation. Henry M. Thomas, Jr., M.D., Baltimore 571

Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia. C. W. Baldridge, M.D., and Adelaide Barer, Ph.D., Iowa City 589

Treatment of Polycythemia Vera (Erythremia) with Solution of Potassium Arsenite. Claude E. Forkner, M.D.; T. F. McNair Scott, M.R.C.P. (Lond.), and S. C. Wu, M.D., Boston 616

Diagnosis of Obscure Cases of Pernicious Anemia. R. T. Beebe, M.D., and M. M. Wintrobe, M.D., Baltimore 630

Book Reviews 638

PAGE

MAY, 1933. NUMBER 5

Hydrophobia: Report of Two Fatal Cases with Pathologic Studies in One. David Riesman, M.D.; W. W. Fox, M.D.; B. J. Alpers, M.D., and David A. Cooper, M.D., Philadelphia 643

Treatment of Secondary Anemia, with Special Reference to the Use of Liver Extract Intramuscularly. William P. Murphy, M.D., Boston..... 656

Avitaminosis in Natives of Rhodesia: Treatment of Epidemic Scurvy by the Intravenous Injection of Citrus. T. J. Dry, M.A., M.B., Ch.B., Rochester, Minn..... 679

Bronchial Disinfection and Immunization: II. The Effects in Rabbits of Intrabronchial Injections of Vaccines, Bacteriophage and Antivirus. John A. Kolmer, M.D., Philadelphia..... 692

Experimental Edema in Nephrectomized Dogs: III. Serum Proteins and Effusion Fluids. C. J. Farmer, M.A.; F. S. Barry, M.S., M.B.; Alice Reed, M.S., and A. C. Ivy, M.D., Chicago..... 704

Cardiospasm, with a Review of the Literature. Mills Sturtevant, M.D., New York 714

Mode of Production of the First Heart Sound. William Dock, M.D., San Francisco 737

Cytoplasmic Changes in Circulating Leukocytes in Infection. Charles J. Sutro, M.D., New York..... 747

Syphilis of the Stomach, with Special Reference to the Significance of Spirochetes. Harry A. Singer, M.D., Chicago..... 754

Experimental Coronary Occlusion: Inadequacy of the Three Conventional Leads for Recording Characteristic Action Current Changes in Certain Sections of the Myocardium; an Electrocardiographic Study. Francis Clark Wood, M.D., and Charles C. Wolferth, M.D., with the Technical Assistance of Mary M. Livezey, A.B., Philadelphia..... 771

Immune Reactions in Diabetes. Johannes K. Moen, M.D., and Hobart A. Reimann, M.D., Minneapolis 789

Effect of Anoxemia on the Emptying Time of the Stomach. Edward J. Van Liere, Ph.D., M.D.; George Crisler, Ph.D., M.D., and Dennis Robinson, B.S., Morgantown, W. Va. 796

Consumption of Blood Sugar by Muscle in the Nondiabetic and in the Diabetic State. Wallace M. Yater, M.D.; J. Markowitz, M.D., and Russell F. Cahoon, B.S., with the Technical Assistance of W. H. Burrows, Washington, D. C. 800

News and Notes 814

Book Reviews 815

JUNE, 1933. NUMBER 6

Mechanism of Edema of the Renal Type: Study on Basis of Changes in Water Content of Blood and in Protein Content of Blood Plasma During Cycle of Edema in Children. William B. McClure, M.D.; Carol Beeler de Takáts, B.S., and Winifred Franz Hinman, M.S., Chicago..... 819

Congestive Heart Failure and Angina Pectoris: The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity. Herrman L. Blumgart, M.D.; Samuel A. Levine, M.D., and David D. Berlin, M.D., Boston..... 866

Nature of Skin Reactions Produced by Heat-Inactivated Poliomyelitis Virus: Reaction of Persons Convalescing from Poliomyelitis and of Normal Persons to Intracutaneous Injections of the Heat-Inactivated Virus. Albert B. Sabin, M.D.; William H. Park, M.D., and Claus W. Jungeblut, M.D., New York 878

Excretion of Nitrogen by Obese Patients on Diets Low in Calories, Containing Varying Amounts of Protein. Robert Wood Keeton, M.D., and Dorothy Dickson, A.B., Chicago..... 890

JUNE—Continued

PAGE

Histamine Test Meals: An Analysis of Nine Hundred and Eighty-Eight Consecutive Tests. W. Scott Polland, M.D., San Francisco 903

Peptic Ulcer: VIII. Results of Medical and Surgical Treatment of Patients in Rural Districts and in Small Towns. Charles Bruce Morton, M.D., University, Va. 920

Effect of Stimulation of Visceral Nerves on Coronary Flow in Dogs. Josephine Hinrichsen, M.S., and A. C. Ivy, Ph.D., M.D., Chicago 932

Auricular Flutter with Complete Auriculoventricular Block in a Patient with Coronary Disease. Aaron E. Parsonnet, M.D., C.M., and Sol Parent, M.D., Newark, N. J. 938

Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage. Arthur M. Hoffman, M.D., and Everett Delong, M.D., Los Angeles 947

Electrocardiographic Studies of the Dying Human Heart, with Observations on the Intracardiac Injection of Epinephrine: Report of Twenty-Five Cases. J. Fletcher Hanson, M.D.; W. K. Purks, M.D., and Ruskin G. Anderson, M.D., Atlanta, Ga. 965

Diffuse Amyloidosis: Three Unusual Cases; a Clinical and Pathologic Study. Edwin G. Bannick, M.D.; John M. Berkman, M.D., and Donald C. Beaver, M.D., Rochester, Minn. 978

Book Reviews 991

General Index 995

Archives of Internal Medicine

VOLUME 51 JANUARY, 1933 NUMBER 1

SYNDROME OF ANEMIA, GLOSSITIS AND DYSPHAGIA

REPORT OF EIGHT CASES, WITH SPECIAL REFERENCE TO OBSERVATIONS AT AUTOPSY IN ONE INSTANCE

M. M. SUZMAN, M.D., M.R.C.P. (LOND.)
Medical Research Fellow, Rockefeller Foundation; Research Fellow in Medicine, Massachusetts General Hospital and Harvard Medical School
LONDON, ENGLAND

The association of dysphagia, superficial glossitis and anemia has been noted sufficiently frequently during the past few years to have become regarded as a clinical entity, and has often been referred to as the "Plummer-Vinson syndrome." Since none of the many hypotheses concerning the nature of this condition appears to have been based on histopathologic data, it was thought that a report of the observations at autopsy in one instance might prove of value. In addition, a review of the literature and the clinical findings in eight cases of this syndrome are presented.

The syndrome was first pointed out independently by Brown Kelly [1] and by D. R. Paterson [2] at the summer congress of the Laryngological Section of the Royal Society of Medicine in London, May 2, 1919, with papers entitled, respectively, "Spasm at the Entrance of the Oesophagus" and "A Clinical Type of Dysphagia."

The condition, as described by these writers, was confined to women of middle age. Anemia, dyspepsia and impaired general health were notable features and occasionally preceded the dysphagia, which, referred to the level of the larynx, had often been present for years. The onset, although usually gradual, was occasionally sudden, being first noticed when a particle of food became lodged in the throat. Although intervals of freedom from symptoms occasionally occurred early in the course of the disease, these intervals gradually diminished until the dysphagia became constant. As a result, mastication of necessity became thorough, and swallowing careful, slow and tedious, and the diet was reduced to semisolids and liquids. Frequent catching of food at the entrance to the gullet occurred, with distressing efforts to dislodge it, referred to as "choking spells." A longer time was taken at meals, what is known as

From the Medical Services of the Massachusetts General Hospital, Boston.

1. Kelly, A. B.: J. Laryng. & Otol. **34**:285, 1919.
2. Paterson, D. R.: J. Laryng. & Otol. **34**:289, 1919.

a "small swallow" thus developing. Becoming apprehensive and nervous for fear of choking, these patients thus preferred solitude during meals.

The mucous membrane of the mouth and tongue exhibited a smooth, glossy appearance, the latter being devoid of papillae. Fissures were present at the angles of the mouth, due, according to Kelly, to the increased salivation dependent on the esophageal obstruction (Rogers' salivary-esophageal reflex). This condition was found to have extended to the pharynx, the hypopharynx and occasionally the upper section of the gullet. In these situations the mucosa, which was pale and dry, was also very thin, special care being necessary during instrumentation to avoid producing a crack, the mucosa having lost the suppleness and resiliency which permits the cricoid being tilted forward to get a good view of the introitus. The deepest part of the hypopharynx did not present the usual sphincter-like appearance. Instead of rounded folds or cushions of mucous membrane forming a stellate arrangement, tense bands passed in various directions with their thin edges tightly pressed together. The entrance to the esophagus appeared as a pinhole or small irregular opening, or as an obliquely placed slit, and was not always in the midline. Sometimes half of the mouth of the gullet seemed closed by a web passing backward from the cricoid. Paterson noted that the buccal and tongue mucosa exhibited a thinning of the superficial epidermal layer and an apparent thickening from infiltration of the underlying tunica propria. The appearance was not unlike that of a condition due to syphilis, but negative Wassermann reactions and the failure of improvement under antisyphilitic treatment ruled out this disease. Since pressure on the folds of mucous membrane caused them to fall apart during instrumentation, Kelly was of the opinion that the stenosis was due to their firm approximation and not to organized adhesions. These writers stressed the spasmodic nature of the obstruction, and in this connection Kelly mentioned as a possible etiologic factor inflammatory involvement of the nerve supply causing hyperesthesia of the sensory side (Meissner's plexus) or stimulation of the motor side (Auerbach's plexus), both of which phenomena would lead to spasm. The tendency of cancer to supervene was pointed out, Kelly also commenting on the fact that 75 per cent of cancers of the upper end of the esophagus occur in women. Concerning the neurosis, so commonly present, Brown Kelly did not regard these patients as being primarily neurotic, since before the onset of the difficulty in swallowing they had been quite normal in this respect. Treatment consisted of the passage of an esophagoscope.

In 1922, Porter P. Vinson,[3] in a paper entitled "Hysterical Dysphagia," reported sixty-nine cases from the Mayo Clinic. In this

3. Vinson, P. P.: Minnesota Med. **5**:107, 1922.

series of patients, of whom 51 were males and 12 females, the onset of the dysphagia was usually sudden, often dating from a choking attack brought about by a piece of solid food lodged high in the throat. A moderate secondary anemia developed, thought by this writer to be due probably to the quality of the food which these patients were obliged to consume. In thirty-seven of the patients the hemoglobin content was below 60 per cent, the lowest reading being 27 per cent. Splenomegaly was noted in twelve instances. Roentgen examination of the esophagus showed nothing abnormal. It is interesting to note that in contrast to the findings of Kelly and Paterson, endoscopic examination did not reveal anything regarded as abnormal, nor were lesions of the mouth or tongue noted. Treatment consisted of the passing of a plain esophageal sound (size immaterial) into the stomach, guided by a previously swallowed silk thread, reassurance of the patient that he would be able to swallow forthwith, and the administration of iron and arsenic. Under this therapy, in addition to shrinking of the spleen, the blood picture improved at once, and became normal if the symptoms did not eventually recur—which was not unlikely if the patients were not constantly reassured with regard to their condition. Concerning the dysphagia, Vinson was of the opinion that the treatment was purely suggestive, as it entailed no real stretching of the esophagus. An interesting observation, pointed out by Plummer,[4] in patients who had been relieved of their dysphagia and were taking food freely, was the development of a moderate degree of hypothyroidism, which necessitated the administration of thyroxine. In explanation of this, it was suggested that during long periods of inanition a slight demand for thyroxine results in atrophy of the thyroid from disuse; hence, following the relief of the dysphagia, this organ may not be able to meet the metabolic demands of the body.

In 1926, Moersch and Conner[5] of the Mayo Clinic, reported on sixty-five cases of this syndrome. All the patients were women between the ages of 23 and 63 years, the average being 45; they had suffered from the disease for periods varying from one month to thirty-four years, the average duration being eight years. The onset was usually sudden. Loss of weight, occurring in about half of the cases, was not marked, averaging only 8 pounds (3.6 Kg.). The mucous membrane of the mouth was atrophic and dry, and cracks at the corner of the mouth and glossitis were occasionally noted. A large number of the patients were edentulous. No organic lesions, such as webs or membranes, were noted in the esophagus, the mucous membrane of which, however, was dry, atrophic and inelastic, tending to bleed easily. Splenomegaly was noted in twenty of the sixty-five cases. The average figures for the

4. Plummer, cited by Vinson.[3]

5. Moersch, H. J., and Conner, H. M.: Hysterical Dysphagia, Arch. Otolaryng. **4**:112 (Aug.) 1926.

red blood cell counts, hemoglobin concentrations and color indexes were, respectively, 3,800,000, 48 per cent and 0.6. There were no significant alterations in the total or differential counts of the white blood cells. Of the ten instances in which a gastric analysis was performed, achlorhydria was present in eight. Paresthesia of the extremities was a feature in five cases. The treatment used by these physicians was identical with that advocated by Vinson, much importance being attached to the processes of suggestion and reassurance. They regarded the syndrome as being a fundamental disturbance primarily involving deglutition, dependent on some nervous or psychic strain, and they believed that the anemia and splenomegaly were probably the result of the prolonged unbalanced diet arising from the difficulty in swallowing. They suggested, in view of the occasional precedence in time of the anemia, glossitis and stomatitis over the dysphagia, that the latter may well be due to irritation of the entrance to the gullet by the esophagitis associated with the preexisting inflammatory lesions of the mouth. They also pointed out some similarity of this disease to pernicious anemia, and suggested that both diseases may have a common fundamental deficiency factor.

In 1926, A. F. Hurst [6] reported a single case, in which the anemia antedated the difficulty in swallowing by two years. Paresthesia, splenomegaly and a "streptococcal glossitis" were present. The anemia was microcytic and hypochromic, the average diameter of the red blood cells being 6.82 microns and the color index below unity. Roentgen examination revealed considerable hesitation in the passage of food from the pharynx into the esophagus. It was impossible to pass an esophagoscope or mercury bougie owing to tight spasm of the sphincter. The patient improved considerably on the administration of iron, although the dysphagia did not disappear entirely. This writer was of the opinion that the anemia and splenomegaly were due to the streptococcal infection rather than the result of an unbalanced diet dependent on the dysphagia, and further, that the latter was due to a reflex spasm caused by local inflammation produced by the same streptococcal infection which led to glossitis.

Ryle,[7] in 1928, reported a case of esophageal spasm with severe anemia, the onset of which took place shortly after a confinement. Recurrent superficial ulceration of the tongue was a feature, but there were no organic lesions in the throat. The dysphagia was relieved by esophagoscopy, and the anemia by the administration of iron and arsenic. The writer was of the opinion that the difficulty in swallowing was hysterical, that the anemia had been initiated by sepsis associated

6. Hurst, A. F.: Guy's Hosp. Rep. **76**:426, 1926.
7. Ryle, J. A.: Guy's Hosp. Rep. **77**:33, 1927.

with the confinement and was perpetuated by the poor diet, and that the condition of the tongue was that of a streptococcal glossitis.

Jones and Owen,[8] in 1928, reported on a series of cases, the findings in which were essentially similar to those described by previous writers, including a normal white blood cell picture. They confirmed the esophageal appearances noted by Kelly and Paterson, stating that the lumen of the intestine may be greatly reduced by a thin membranous web or that tense bands of raised thinned mucosa may pass in various directions. They pointed out, however, that the esophageal opening was occasionally very lax with no sphincter-like action. The x-ray findings presented nothing of note except an occasional slight hesitation in the passage of food into the esophagus. These writers were of the opinion that sepsis was not an etiologic factor.

In 1929, Cameron,[9] in a report of twenty-five cases, all of which were in women between the ages of 41 and 60 years, described the usual buccopharyngeal and blood findings. He noted that hydrochloric acid was present in the stomach in all of the eleven patients on whom a gastric analysis was performed, and that splenomegaly was not an infrequent finding. In regard to the sequence of the symptoms, he noted that in fifteen cases dysphagia preceded the pallor, while in five instances the latter was noticed before the onset of the difficulty in swallowing; in the remaining five cases this point was difficult to decide. The anemia, he suggested, was probably the result of lack of iron associated with the semistarvation brought about by the dysphagia. This writer also thought that perhaps the cause of the difficulty in swallowing may be found in involvement of the nerve endings brought about by inflammatory changes in the mucosa and submucosa. Atrophy of the mucous glands was also cited as a contributing factor. Attention was drawn to the high incidence of cancer at this site in women, and also to the occasional supervention of malignant disease at the entrance to the gullet in this syndrome. Treatment consisted of passing an esophageal dilator and the administration of iron and occasionally of thyroid extract.

Evans,[10] in a paper entitled "Nervous Dysphagia," put forward the view that the underlying cause of this syndrome is tertiary syphilis of the third or fourth generation. To substantiate this hypothesis, this writer cited the occurrence of symptoms of involvement of the central nervous system, cardiovascular changes, such as tachycardia or arrhythmia, and, in addition, lesions of the lips, mouth and tongue, an occasional positive Wassermann reaction and the beneficial effect of antisyphilitic treatment.

8. Jones, A. M., and Owen, R. D.: Brit. M. J. **1**:256, 1928.
9. Cameron, M.: J. Laryng. & Otol. **44**:168, 1929.
10. Evans, G.: Practitioner **124**:317, 1930.

Recently, Witts,[11] in addition to a short review of the literature, reported the findings of this syndrome in thirteen instances, all in middle-aged women, with a mean duration of symptoms of approximately thirteen years. In nine cases the three cardinal symptoms developed simultaneously; in three dysphagia appeared first, while in one the anemia was a feature many years before the onset of the difficulty in swallowing. The usual buccopharyngeal manifestations were also noted. With one exception, the anemia was of the microcytic type throughout, the average figures for red and white blood cell counts, hemoglobin concentration and color index were, respectively, 4,200,000, 7,200, 48 per cent and 0.55. Although the differential white blood cell count, the blood platelet count, the fragility of the red blood cells and the number of reticulocytes were normal, the Arneth counts were noted as having shown a "shift to the left." This condition of the leukocytes tended to disappear coincidently with the improvement in the hemoglobin concentration. One patient was trephined over the upper third of the tibia, but only fatty marrow was obtained. Splenomegaly, present in five of the thirteen patients, disappeared in four during treatment. Of seven patients, only one had a normal gastric secretion; three had complete achlorhydria, one a low amount of free hydrochloric acid and one only a trace. In the remaining case, it is interesting to note that, although achlorhydria and macrocytic anemia were originally present, in a relapse three years later some free hydrochloric acid was found in the gastric contents and the anemia had become microcytic. An important observation in another case was a relapse of the anemia, unaccompanied by a recurrence of dysphagia, after an initial recovery from both these symptoms. Witts treated his patients with iron in large doses and occasionally with transfusion of blood and the passage of esophageal bougies. Administration of liver and diluted hydrochloric acid or of preparations of vitamins B or A, C and D did not seem to influence the anemia, glossitis or dysphagia. The anemia was relatively easily alleviated with iron and then dysphagia became more tolerable and the glossitis usually improved. This writer pointed out the occasional occurrence of mild dysphagia in what he called simple achlorhydric anemia, and the close correspondence of the latter disease with the present syndrome in regard to the age and sex of the patient and to the glossitis and anemia. Other conditions were mentioned, such as sprue, pellagra, chylous diarrhea, stenosis of the small intestine and addisonian pernicious anemia, in which glossitis, anemia and occasionally dysphagia are found. He did not believe that this disease was a result of streptococcal infection (Hurst), that the anemia was due to the dysphagia (Vinson) or that the symptoms were the result of syphilis (Evans).

11. Witts, L. J.: Guy's Hosp. Rep. **81**:193, 1931.

Recently, Paterson,[12] in a communication to the Royal Society of Medicine, confirmed his original observation and views on this subject. His description of the syndrome was essentially similar to that reported in 1919. This writer retained the view that the obstruction is of the nature of a spasm, and that the anemia is a late symptom, secondary to the dysphagia. He stated, however, that from an early stage in the course of the disease some degree of atrophic change may be noted in the mucous membrane of the tongue. Concerning treatment, in addition to instrumentation, the importance of reassurance to the patient regarding the swallowing of solid food was noted. He stressed the frequency with which malignant growths develop in this syndrome.

In the discussion of Paterson's [12] paper, R. S. Johnson pointed out from his experience with six cases that following the passage of bougies, although dysphagia ceased, the rise in hemoglobin concentration was very slow, in some cases taking eighteen months to return to normal figures. In one of his cases the condition of the blood remained unaltered. Marked improvement, however, usually followed the administration of liver extract and of large amounts of iron. It was also noted that achlorhydria and increased fragility of the red blood cells were features of this syndrome.

During the past two years, eight cases of this syndrome have been studied at the Massachusetts General Hospital, one of which proved fatal following an esophagoscopic accident. The reports of these eight cases, together with the autopsy observations in the fatal case, will now be presented.

REPORT OF CASES

CASE 1.—S. M. N., the patient, a woman, single, aged 27, after having suffered from dysphagia for three years, sought treatment when this disability had become almost complete. Esophagoscopy revealed a dimple-like opening to the gullet on the right side just below the cricoid. The opening was dilated by means of a plunger, after which a broken web was seen on the right posteriorly. Examination of the blood showed a red cell count of 4,700,000 per cubic millimeter and a hemoglobin concentration of 50 per cent. Achromia, poikilocytosis and anisocytosis of the red blood cells were noted. Pills of ferrous carbonate, U.S.P. (six daily), and varying amounts of whole liver were administered, much improvement taking place, which was maintained for twelve months; then a relapse occurred. Esophagoscopy, performed again two months later, revealed an esophageal opening, 0.5 cm. in diameter, and a web situated anterolaterally on the left. The tongue showed a superficial atrophic glossitis, and fissures were present at the angles of the mouth. Neither paresthesia nor any symptoms attributable to anemia were present. The red blood cell count was 4,800,000 and the hemoglobin concentration 50 per cent. The Wassermann test was negative. Gastric analysis after histamine stimulation revealed the presence of free hydrochloric acid and low figures for total acidity. Treatment consisted of esophageal dilation and the administration daily

12. Paterson, R. D.: Proc. Roy. Soc. Med. (Sect. Laryng.) **24**:1203, 1931; J. Laryng. & Otol. **46**:532, 1931.

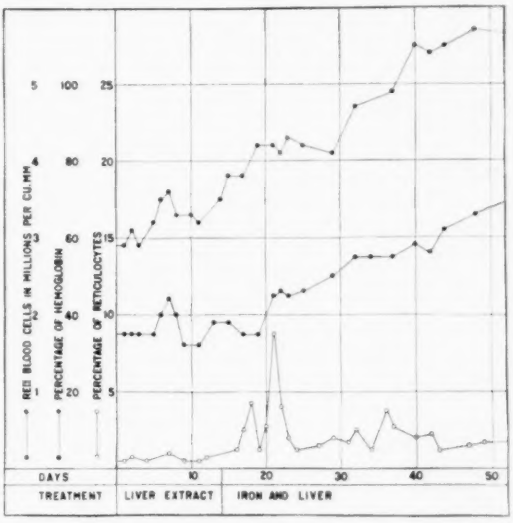
of from 140 to 180 grains (9 to 11.6 Gm.) of iron and ammonium citrate and 2 drachms (7.7 Gm.) of diluted hydrochloric acid (U.S.P.). With this treatment, although the hemoglobin increased only 10 per cent, there was definite general improvement and the fissures at the angles of the mouth healed promptly. The dysphagia, however, persisted and further instrumentation was found necessary to bring about alleviation of this symptom.

Comment.—The early age at which the syndrome developed in this patient is noteworthy, as is also the fact that after she had been relieved of the dysphagia by the breaking of a web in the process of dilation, this symptom recurred one year later, owing to the development of another web at a different site.

Case 2.—M. M., the patient, a woman, aged 60, single, was admitted to the Massachusetts Eye and Ear Infirmary complaining of difficulty in swallowing of one year's duration, and of loss of weight amounting to 18 pounds (8.1 Kg.) in the past seven months. On roentgen examination it was observed that the barium passed to the left through the upper end of the esophagus, the right side being obstructed, and that a web was present immediately below this site. Esophagoscopy revealed a constriction consisting of an anteroposterior band dividing the entrance to the esophagus into two parts. This band was broken, the esophagus then being easily dilated with a large bougie (gage 36). No examination of the blood was performed at this time. The patient was discharged symptom-free and remained well for four months. Then the dysphagia returned, again necessitating the passing of an esophageal bougie, which resulted in relief from symptoms for a period of four months. In addition to dysphagia, the patient forthwith commenced to suffer from general weakness, dyspnea on exertion, numbness and tingling in the hands and feet, and a sore mouth and tongue. She also noticed that she had become very pale, although some degree of pallor was alleged to have been always present. These symptoms having progressed for a period of three months, the patient was admitted to the Medical Services of the Massachusetts General Hospital in an emaciated condition. The skin was pale with a yellow tinge, the lips were cracked and fissured, and the tongue showed a marked superficial atrophic glossitis, being extremely smooth and glossy. Examination of the blood showed a red cell count of 2,900,000, a hemoglobin concentration of 35 per cent and a white blood cell count of 13,100, with a polymorphonuclear leukocytosis. The red cells were achromic and showed alteration in size and shape, the average diameter being 6.5 microns with a dispersion of 1.4 microns. The blood platelets appeared to be diminished. The icteric index was 3. Serum calcium and phosphorus estimations were, respectively, 8.24 and 4.02 mg. per hundred cubic centimeters of blood. The serum protein was 6.9 per cent. The Wassermann and Hinton tests were negative. Gastric analysis revealed a complete absence of free hydrochloric acid after histamine stimulation. The basal metabolic rate was +11 per cent. At roentgen examination a slight narrowing at the entrance to the esophagus was noted. After an esophageal bougie had again been passed, treatment consisted, at first, of the daily administration of liver extract no. 343, N.N.R., the amount derived from 600 Gm. of liver, for a period of eleven days. During this time no significant changes occurred in the numbers of red blood cells and reticulocytes, in the hemoglobin concentration or in the condition of the lips, mouth and tongue, which were extremely sore. However, when 90 grains (5.8 Gm.) of iron and ammonium citrate, together with a half-pound (227 Gm.) of prepared liver pulp, was administered daily, marked improvement occurred, not only in the condition of the mouth

and tongue but also in the red blood cell count and hemoglobin concentration, which, over a period of thirty-five days, increased to 5,700,000 and 65 per cent, respectively. The reticulocytes responded and reached a peak of 8.6 per cent on the eighth day after liver and iron were first given. The patient was discharged entirely free from symptoms (see chart).

Comment.—It should be noted that thirty years previously this patient had suffered from a chronic gastric ulcer, for which a gastroenterostomy had been performed (compare cases reported by Witts [11] and by Davies; [19e] also case 5 in the present series). It is noteworthy that whereas no improvement resulted from the relief of the dysphagia by



The effect of the daily administration of liver extract no. 343 N.N.R. (amount derived from 600 Gm. of liver), and of iron and ammonium citrate (3 Gm.) together with whole liver (220 Gm.) in a case of the "Plummer-Vinson Syndrome" (case 2).

instrumentation and the administration of liver extract, relief of the blood condition and of the soreness of the tongue followed promptly when iron was given in addition to liver.

Case 3.—H. M. F., the patient, a married woman, aged 45, was admitted to the medical services of the Massachusetts General Hospital complaining of difficulty in swallowing of twenty years' duration, and of having been pale for the past thirty years. She did not remember whether the onset of the dysphagia was sudden or gradual, or whether there was any nervous shock or special incident which precipitated her symptoms. The dysphagia was referred to the level of the thyroid and was present at all meals and worse when she felt nervous and when she was watched. Solid food tended to stick, occasionally necessitating regurgita-

tion. On one occasion a pea lodged for several days in her throat, preventing her from swallowing even liquids. There was no pain, substernal distress, nausea, vomiting, hematemesis, diarrhea or tarry or bloody stools. Her diet was thus limited, consisting chiefly of fruit juices, beverages, milk and milk products, eggs and carefully prepared cereals and vegetables. Eight years previously, she noticed that her skin was yellow for a period of one year. Soreness of the mouth and tongue, worse at night and while eating, was first experienced three years previously. There were no neurologic symptoms, such as numbness and tingling of the extremities or difficulty in walking. During the past twenty years, she had lost 33 pounds (14.9 Kg.). She had been pregnant six times.

On examination, the tongue, which appeared small and atrophied, showed a marked superficial atrophic glossitis, being smooth and shiny. The right side was especially red and inflamed. On the under surface there were small grayish areas, not raised or hard, but somewhat tender. The patient was unable to protrude the tongue far because, on attempting this, severe pain was experienced. Moreover, it appeared that the tongue was somewhat fixed. The buccal mucous membrane showed shiny red areas, on which was superimposed a leukoplakia-like condition. The gums were spongy and the lips dry, with fissures at the angles of the mouth. Esophageal examination revealed a stricture at the entrance to the esophagus, the lumen at this site being one-third its normal size. On roentgen examination, there was an irregular constriction in the upper end of the esophagus, beginning about 1 inch (2.5 cm.) below the entrance and extending for a distance of 1½ inches (3.8 cm.), reducing the lumen to one-third its normal diameter.

The red blood cells numbered 4,200,000, and showed moderate achromia and alteration in size and shape. The average diameter was 7.4 microns, with a dispersion of 1.2 microns. The hemoglobin concentration was 60 per cent. The total and differential white blood cell counts were normal. Apart from the presence of a few blood cells in the urine for a period of a few days, the urine was essentially normal. The Wassermann and Hinton tests were negative. The basal metabolic rate was +3 per cent. A tube could not be passed for the purpose of a gastric analysis. Microscopic examination of a smear taken from the mouth did not reveal Vincent's organisms.

Treatment consisted of the daily oral administration of liver extract for a period of one month (no. 343, the amount derived from 600 Gm. of liver, replaced later by 2 ounces [59.1 Gm.] of E.49 Valentine). No improvement in the buccopharyngeal or the blood condition having taken place from the use of liver extract, the esophageal introitus was dilated on two occasions. This procedure caused so much pain that the patient was unable to eat or drink for several days and lost 7 pounds (3.1 Kg.). Improvement in swallowing occurred later, however, and a diet of high caloric content was instituted. No change was noted in the blood, and the patient was discharged. During the next few months, although the administration of 60 grains (3.8 Gm.) daily of iron and ammonium citrate together with liberal amounts of liver extract brought about a slight increase in the number of red blood cells and in the percentage of hemoglobin, no improvement was noted in the buccal lesions. A biopsy was therefore performed on the scarlike tissue of the right side of the tongue and of the anterior pillar of the fauces. This showed a squamous cell carcinoma. This observation necessitated the resection of the right anterior pillar of the fauces and a portion of the base of the tongue and of the buccal mucosa, in addition to a block dissection of the glands of the neck. A recurrence occurred later, for which roentgenotherapy was employed.

Comment.—The importance of this case lies in the continued severity of the lesions of the tongue, mouth and pharynx in spite of treatment

with liver and iron and by instrumentation, and the subsequent development of malignant disease at these sites. It is notworthy that neither the administration of liver extract nor relief of the dysphagia brought about improvement in the condition of the blood, whereas, when iron was given, a slight, though definite, increase took place in the number of red blood cells and in the hemoglobin concentration.

Case 4.—B. H. F., the patient, a married woman, aged 46, was admitted to the Massachusetts General Hospital complaining of difficulty in swallowing, dryness of the mouth and throat, loss of strength, shortness of breath and palpitation. These symptoms had existed for four years. The dysphagia was referred to the level of the thyroid and was more severe when the patient swallowed solids than when she swallowed liquids. The tongue was not sore, nor were paresthesias present.

On examination, the tongue showed atrophy of the mucous membrane, which was smooth and shiny. Cracks and fissures were present at the corners of the mouth, and the patient was edentulous. Roentgen examination revealed a constriction at the entrance to the esophagus. The red cell count was 3,800,000, the hemoglobin concentration 55 per cent and reticulocytes 1 per cent. The red blood cells showed achromia, rare polychromatophilia and distinct alteration in size and shape. The total and differential white blood cell counts were considered normal. The icteric index was 5. The Hinton blood test was negative. Gastric analysis, after histamine stimulation, revealed a complete absence of free hydrochloric acid and a low content of combined acid. The urine was not abnormal. Treatment, consisting of the administration of iron and ammonium citrate (90 grains daily), a high caloric diet and dilation of the esophageal stricture, brought about distinct improvement both in the blood condition and in ability to swallow.

Comment.—Since the dysphagia and the symptoms attributable to anemia appeared simultaneously, and as it takes time for enough anemia to develop to cause palpitation and dyspnea, it is almost certain that some degree of anemia had been present before the onset of the difficulty in swallowing.

Case 5.—K. H. G., the patient, a married woman, aged 53, was admitted to the Massachusetts General Hospital complaining of general muscular weakness, palpitation, dizziness, nausea, vomiting and a yellowish pallor of the skin, all of four years' duration, although more marked during the past year. During the past four months sores had frequently appeared on her lips. Two years before the onset of these symptoms, a laparotomy had been performed on account of marked abdominal pain with nausea and vomiting. A gastric ulcer was found, for which a sleeve resection of the stomach and a posterior gastro-enterostomy were performed, resulting in much relief. It should be noted that there had been no complaint of difficulty in swallowing.

Studies of the blood revealed a red cell count of 2,400,000 and a hemoglobin concentration of 40 per cent. A considerable degree of achromia was present, with marked poikilocytosis and moderate anisocytosis. Although macrocytes were present, they were not well filled with hemoglobin. Some degree of polychromasia was noted. The total and differential white blood cell counts were normal, and the blood platelets were diminished in number. Examination of the urine yielded negative results. The gastric contents contained no free hydrochloric acid and small amounts of combined acid. The spleen and liver were palpable. The tongue

was smooth and devoid of papillae. In the course of a roentgen examination of the gastro-intestinal tract, it was observed that the esophagus presented no abnormality. Treatment consisted of transfusion of blood and the administration of a diet of high caloric content.

Seven years later, this patient returned to the hospital complaining of occasional attacks of vomiting and diarrhea, and of difficulty in swallowing of three years' duration, the obstruction being referred to the level of the thyroid and encountered only with solid food. The tongue was small and atrophic with a smooth and shiny mucous membrane, totally devoid of papillae. Fissures were present at the corners of the mouth. The spleen was palpable, but the liver was not enlarged. Examination of the central nervous system revealed nothing abnormal. Anemia was still present, the red blood cell count being 3,500,000 and the hemoglobin concentration 40 per cent. There was marked achromia with much alteration in the size and shape of the red blood cells. Treatment, consisting of the administration of 90 grains daily of iron and ammonium citrate, was instituted. Unfortunately, however, up to the time of writing, no data were available concerning the effects of this therapy.

Comment.—This case is of especial importance, first, in that two years after a partial gastrectomy with gastro-enterostomy, there developed a hypochromic anemia with atrophy of the mucous membrane of the tongue, and second, in that the latter features antedated the dysphagia by four years. It is obvious, therefore, that in this case the anemia was not the result of a restricted diet dependent on the difficulty in swallowing.

Case 6.—A. F. M., the patient, a woman, aged 58, was admitted complaining of numbness and tingling of the fingers for two years and of the toes for six months. Shortness of breath on exertion, dizziness and general weakness had been features for several months, and weakness and stiffness of the legs for two months. Indigestion, with occasional attacks of nausea, vomiting and diarrhea, had been present for many years. The patient stated that she had had no meat for fifteen years, having lived chiefly on eggs, bread and vegetables. The tongue had never been sore. Mild difficulty in swallowing, referred to the level of the thyroid and encountered only with solids, had been developing gradually for several months. The mucous membrane of the tongue showed a moderate degree of atrophy, being smooth and shiny chiefly along the edges. Roentgen examination revealed a constriction at the upper end of the esophagus. No abnormal physical signs were revealed on examination of the nervous system, nor was the cerebrospinal fluid abnormal. A tube could not be passed for the purpose of a gastric analysis. Studies of the blood revealed a red blood cell count of 4,500,000 and a hemoglobin concentration of 60 per cent. The red blood cells were somewhat achromic and varied in size and shape. The total and differential white blood cell counts were normal. Esophageal dilation brought about much improvement in swallowing.

Comment.—This case is of interest in that intense paresthesia of the extremities was complained of, and this in spite of the mild degree of anemia present. Although no organic neurologic abnormalities were found on examination, definite difficulty in walking was a feature; this may well have been due to the severe numbness and tingling.

CASE 7.—A. O. B., the patient, a married woman, aged 61, was admitted complaining of difficulty in swallowing solid food for seven years. The diet had become progressively limited, and had consisted for about two years chiefly of milk, cream, eggs and meat and fish broths. For the past five years she had experienced gradually increasing weakness, attacks of dizziness, dyspnea, palpitation and swelling of the ankles. Constipation had alternated with attacks of diarrhea for the past two years. Soreness and tenderness of the lips, tongue and throat, cracking of the angles of the mouth and numbness and tingling of the fingers and toes on exposure to cold had been features during the past twelve months. There had been no nausea or vomiting, and the appetite had remained good. She had had six children, two of whom died within a few months of birth, and, in addition, two miscarriages.

On examination, the patient appeared pale, thin and undernourished with a yellow tint to the skin. The nails were spoon-shaped, with longitudinal splitting and striations. Cataracts were present in both eyes. There were fissures at the angles of the mouth; the tongue was small and atrophic, and the mucous membrane smooth, tender and devoid of papillae. Edema of the feet and lower part of the legs was present. The spleen was not palpable, but the liver was enlarged, the lower edge being palpable 3 cm. below the costal margin. Studies of the blood showed a marked anemia, with a red cell count of 1,800,000 and a hemoglobin concentration of 15 per cent. There were marked achromia and marked alteration in size and shape of the red blood cells. Macrocytosis was not a feature. A leukopenia was present, the white blood cell count being 3,000. The differential count, however, was not abnormal. The serum protein was 6.3 per cent, and the nonprotein nitrogen content 23 mg. per hundred cubic centimeters of blood. The urine contained a trace of albumin and numerous pus cells. The Wassermann reaction was negative and the blood pressure 142 systolic and 70 diastolic. Gastric analysis, after histamine stimulation, revealed the absence of free hydrochloric acid. Treatment consisted of the intramuscular administration of 900 mg. of ferric citrate over a period of three days. The percentage of reticulocytes rose to 7.6 on the sixth day, and after two weeks the number of red blood cells had increased to 2,500,000 and the hemoglobin concentration to 23 per cent. The further intramuscular administration of 1,600 mg. of iron citrate over a period of four days evoked a second reticulocyte rise with a peak of 5.6 per cent on the sixth day; the red blood cell count and hemoglobin concentration continued to increase, reaching 3,000,000 and 35 per cent, respectively, on the twentieth day after the second course of iron. Marked improvement in the lesions of the lips and tongue was noted. Regeneration of papillae on the tongue, previously completely denuded, was a striking feature. Further, although no instrumentation had been resorted to, the difficulty in swallowing was somewhat alleviated.

Comment.—The unusual severity of the anemia and the well marked spoon-shaped deformity with longitudinal splitting of the nails are notable features in this case. The fact that regeneration of lingual papillae occurred with iron therapy is of importance, in that it may throw some light on the underlying nature of this syndrome.

CASE 8.—E. M. F., the patient, a woman, aged 48, single, was admitted complaining of occasional nausea and vomiting, of a feeling of fulness after eating and pressure in the chest for the past ten years, and of having passed bright blood by rectum at intervals for six years. About four years before admission she commenced to have difficulty in swallowing solid food, numbness and tingling of the

fingers and toes, slight unsteadiness on walking, dyspnea on exertion, palpitation, dizziness and swelling of the ankles. She had lost 15 pounds (6.8 Kg.) in the past two years. Although her tongue had never been sore, she occasionally suffered from painful "cankers" in the mouth. Her diet, necessarily limited, had included little meat or vegetables. She did not remember the duration of her pallor.

On examination, the patient appeared pale, undernourished and poorly developed, with a slight icteric tinge of the skin and conjunctivae. There were fissures and scars at the angles of her mouth. The tongue appeared small and shriveled, and the mucous membrane presented a pale, smooth, somewhat glazed appearance, being devoid of papillae. The buccal mucosa was similarly pale and smooth. The patient was edentulous. The spleen and liver were not palpable. Examination of the blood revealed a moderate degree of hypochromic anemia. The red blood cells numbered 3,500,000, of which 0.8 per cent were reticulocytes. The hemoglobin concentration was 30 per cent, and the total and differential white blood cell counts were normal. The red blood cells appeared achromic, with much variation in size and shape. Examination of the urine and the Hinton blood test yielded negative results. The stools contained occult blood. Although the basal metabolic rate was —33 per cent, no hypothyroid symptoms were present. Fluoroscopic examination of the esophagus revealed an obstruction at the level between the sixth and seventh cervical vertebrae; this was considered to be due to a constricting band or web. Esophagoscopy (performed in the Nose, Throat and Ear Department), revealed a stricture immediately below the entrance to the esophagus. The constriction was dilated by means of bougies, the last of which met with some resistance, and slight bleeding was noted at the tip of the bougie after removal.

The day following endoscopy, the patient complained of pain between the shoulders, and, on examination, subcutaneous emphysema was detected above the clavicle. Two days later, roentgen examination of the chest revealed fluid at the base of both lungs, consolidation in the right lung and air in the mediastinum. Fever developed and the temperature was 101.6 F. The pulse rate had increased to 100 per minute, and a polymorphonuclear leukocytosis with 29,000 white blood cells per cubic millimeter was present. On the fourth day there was much respiratory distress, and a physical examination pointed to the presence of much fluid in the right side of the chest. The following day, the respiratory rate having increased to 60 and the pulse rate to 135 per minute, with much distress, paracentesis of the right side of the chest was performed, and 1,400 cc. of hazy fluid was removed. This contained numerous polymorphonuclear cells and gram-positive cocci in short chains. The patient died the following day.

Autopsy.—The autopsy was performed by Dr. John I. Bradley two and one-half hours post mortem. The body was small, poorly developed and undernourished. Slight pitting edema of the lower extremities was present. Large hemorrhoidal masses were noted. There was only a small amount of subcutaneous fat. No gross pathologic abnormalities were noted in the pericardial or peritoneal cavities, heart, gastro-intestinal tract, bile ducts, spleen, pancreas or its ducts, suprarenals, kidneys, bladder or thyroid gland. In the liver, which weighed 1,900 Gm., two small circumscribed, rounded, yellowish nodules were noted; these resembled the liver tissue as seen in the nodular areas of regeneration. The right pleural cavity contained approximately 800 cc. of thin, turbid, yellowish, purulent fluid. The pleural surfaces were coated with a thin layer of fibrin. An irregular, ragged, oval perforation was present in the mediastinal pleura near its center. Thick, purulent, yellowish fluid could be expressed through this perforation. The left pleural cavity showed no abnormality, except a few slight adhesions in the

lower lateral and posterior portions. The right lung was smaller than the left, and much firmer and less crepitant than normal, having a doughy consistency. No definitely consolidated areas were palpable. The cut surface was homogeneous throughout and light pinkish-gray, and exuded considerable thin frothy fluid. A few small, slightly elevated grayish patches were present in the central portion of the lower lobe. The left lung was normal except for moderate edema and congestion. The aorta and pulmonary artery showed slight atheromatous deposits. The ovaries were normal in size, one containing a single follicular cyst and the other a small fibromatous mass. The uterus was normal except for several small intramural fibroids.

Tongue.—Along both sides and over most of the superior surface of the tongue the mucosa was smooth, glistening and whitish in appearance. The whole organ was thin and atrophic. The papillae were absent, except at the tip and in the central portion of the superior surface.

Esophagus.—Extending along the lateral and posterior surfaces of the esophagus from the level of the larynx to the diaphragm, there was a well defined, narrow, irregular space, measuring roughly 3 cm. in width and 1.5 cm. in depth, which contained thick, yellowish, purulent fluid. There was no gross defect in the wall of the esophagus. On probing the superior esophageal orifice with the little finger a definite constriction was noted, although no obstructing band was seen.

On opening the esophagus there was seen on the anterior and left lateral surface of the esophageal wall just below the introitus and lying over the left posterior portion of the larynx, just below the left pyriform sinus, a relatively large, irregularly triangular area, roughly 2.5 by 1.5 by 2.5 cm. in area, which appeared sharply demarcated from the adjacent normal mucosa. The surface of this area was smooth and yellowish white, but less smooth and glistening than the adjacent mucosa.

At the lateral and posterior margins of the triangular area described, there was a small free fold of mucosa, which could be brought over to the region of the upper right central apex of the triangular area. When this was done, the apparent defect in the mucous membrane was closed. The appearance suggested that this was the relationship before instrumentation and that the esophageal obstruction had been due to a mucosal band, narrowing the lumen of the esophagus in the first portion along the left side.

At the inferior apex of the triangle there was a definite fold of mucous membrane extending across from the anterior central to the left lateral portion of the lumen. A blunt probe inserted in the pocket anterior to this fold passed easily through the esophageal wall into the superior portion of the para-esophageal mediastinal abscess cavity. The tissues around the outer margins of this defect in the esophageal wall appeared irregularly lacerated, but did not show much gross inflammatory reaction. The remainder of the esophagus showed no definite abnormality, except a slightly elevated, finely granular, whitish patch about 1.5 by 1 cm. in area and 3 mm. in height in the central portion of the esophageal interior.

Bacteriologic Examination.—The blood of the right and left sides of the heart on culture showed a growth of the hemolytic streptococcus. Gram-positive diplococci in chains were noted in the right pleural cavity and mediastinum.

Microscopic Examination.—The heart showed slight perivascular fibrosis. On the pleural surface of the lung there was a thick dense layer of fibrin with polymorphonuclear cells, both of which were also present in the subpleural lymphatics and in many of the alveoli. The liver showed slight central congestion. The liver cells in the centers of the lobules were acidophilic and contained considerable brown pigment. A few small focal areas of necrosis of liver cells and polymorphonuclear

infiltration were seen. There was no evidence of syphilis. The pancreas showed a slight degree of interstitial fibrosis. In the spleen, the pulp contained numerous large immature unrecognized cells, which showed occasional mitotic figures. Numerous normoblasts but no megakaryocytes were seen. The malpighian corpuscles were small and inactive, and the arterioles showed moderate hyaline changes. The kidneys showed no abnormalities except a small amount of hyaline material in some arterioles. The suprarenal glands showed no significant abnormality. In the aorta, moderate fibrous intimal thickening and atheromatous change were noted. The thyroid gland showed a slight diffuse increase in the stroma producing a definite separation of the acini. In the mediastinal tissue, edema, a fibrin deposit and an infiltration with mononuclear cells and polymorphonuclear leukocytes were noted. The bone marrow showed a marked diffuse hyperplasia, with both erythropoiesis and granulopoiesis well represented. There were numerous normoblasts scattered diffusely throughout, without regular grouping. Numerous myelocytes, particularly eosinophilic, were present, and megakaryocytes in more than normal proportions.

Tongue.—The epithelium showed marked keratinization extending even into the deeper layers, and in some areas was markedly thinned. Some degree of desquamation was also present. There was a slight lymphocytic infiltration beneath the mucosa. Large deposits of fat were present between the muscle fibers, and there appeared to be a considerable diminution in the amount of muscle tissue present. Fat granules were noted in the muscle fibers and were aggregated chiefly at the poles of the sarcolemma nuclei. In many of the muscle fibers an increase in the number of sarcolemma nuclei was observed, in some instances being associated with an apparent disappearance of the muscle fibers and an interruption of the continuity of the muscle bundle, which was represented only by lines of scarcolemma nuclei. A few places showed small irregular deeply acidophilic areas suggestive of Zenker's degeneration.

Esophagus.—Sections of the proximal, central and distal portions of the esophagus showed similar changes throughout. The epithelium presented (1) a basal layer and (2) extensive desquamation, of varying degrees, of the hyperkeratinized superficial epithelium. The latter resulted in a marked irregular thinning of the epithelium, leaving at times only a single layer of cells. Where this was the case the cells were long and slender, and projected out radially from the esophageal wall in a brush border, giving the surface a very irregular outline. In other sections the epithelium was composed of rather large cells appearing somewhat immature and containing large vesicular nuclei with occasional mitotic figures, giving an appearance somewhat similar to that of leukoplakia.

The submucosa, mainly in the areas where the epithelium was thinned, showed a moderate degree of infiltration with mononucleated cells, chiefly lymphocytes and plasma cells.

The striated muscle in the proximal portion showed a number of homogeneous, deeply acidophilic hyaline areas suggestive of Zenker's degeneration. The smooth muscle throughout presented marked degenerative changes consisting of shrinkage, loss of normal outline and the presence of numerous small hyaline masses. The latter changes were regarded as being probably postmortem artefacts.

Sections from the very proximal end of the esophagus in the region of the triangular defect in the mucosa showed an area in which the epithelium was missing and the surface covered by a dense fibrin layer. There was marked acute inflammatory infiltration in the adjacent issues. The striated muscle showed extensive changes consisting of disappearance of the normal cross-striations with longitudinal splitting of the fibers and the presence of aggregations of large numbers of nuclei

within the sarcolemma. In some places, collections of nuclei were noted, consisting of as many as from twenty to thirty in apposition.

No abnormalities were discerned in the intermuscular nerve plexus of Auerbach, which was readily identified throughout the whole esophagus, except at the pharyngo-esophageal junction.

The liver was assayed for its vitamin A content by the antimony trichloride method of Carr and Price,[13] using the Rosenheim-Schuster modification of the Lovibond tintometer, and expressing the results in "blue units" per gram of tissue per "centimeter cube" according to the method of Moore.[14] It is of interest to note that small, though significant, amounts of vitamin A were present (69 blue units per gram of liver).

Comment.—It appears that the filiform bougie became caught in a fold of mucous membrane, which it readily perforated, and then passed through the esophageal wall into the mediastinal space. The danger of passing an unguided filiform bougie into the esophagus is thus clearly demonstrated. From the gross findings, it is evident that a real obstruction, brought about by raised folds of mucous membrane, was present.

The mucosa and muscle of the tongue and esophagus showed definite histologic abnormalities, consisting chiefly of hyperkeratinization of the epithelium with areas of desquamation and of degenerative atrophic changes in the underlying muscle. Although there was a moderate degree of infiltration of the submucosa with lymphocytic-like cells, on the whole the condition did not appear to be inflammatory. The possibility that the hyperkeratinization of the epithelium may have been dependent on a deficiency of vitamin A is offset by the detection of significant amounts of this substance in the liver. The presence of areas of mucous membrane, simulating leukoplakia and containing immature cells exhibiting mitoses, is of interest, in view of the tendency of malignant disease to develop (see case 3).

COMMENT

A discussion of the significance of the clinical and pathologic aspects of this syndrome is presented here.

In spite of the frequent occurrence of webs, bands or raised folds of mucous membrane obstructing the esophageal entrance, the majority of writers have tended to regard the esophageal obstruction as being due to spasm, while Hurst[15] has held the view that the nature of the obstruction was that of failure of the pharyngo-esophageal sphincter to relax (i. e., achalasia), rather than that of spasm.

Various reasons have been suggested to explain the alleged spasm or failure to relax of the pharyngo-esophageal sphincter. Vinson,[3]

13. Carr, F. H., and Price, E. A.: Biochem. J. **20**:497, 1926.
14. Moore, T.: Biochem. J. **23**:1267, 1929.
15. Hurst, A. F.: Brit. M. J. **1**:375, 1928.

Moersch and Conner [5] and Ryle [7] regarded the spasm as functional or hysterical in nature. However, in view of the well marked gross and microscopic lesions found in the pharyngo-esophageal region in my case, it seems unnecessary that hysteria be considered in the etiology of this disease. Moreover, other hysterical phenomena are not as a rule present, nor can the dysphagia be cured by purely functional means, although certain physicians have stressed the value of reassurance and suggestion in addition to the usual methods of treatment.

Kelly [1] mentioned the possibility of the presence of inflammatory involvement of the nerve supply in the pharyngo-esophageal region, which he held would tend to cause hyperesthesia of the sensory side or stimulation of the motor side, thus leading to spasm. Similarly, Hurst [15] suggested that there may be involvement of Auerbach's plexus by a direct spread of the inflammation from the mucous membrane to the deep lying plexus, thereby interfering with the normal neuromuscular mechanism, in a way similar to that found in achalasia of the cardia.[16] Cameron [17] was also of the opinion that the local nerve tissue may be involved, but pointed out that, since there is no intermuscular plexus within 2 cm. of this region, the nerve tissue involved must be that of the nerve terminals in the epithelium. However, since there was no evidence of neurologic involvement in the pharyngeal or esophageal tissues in the case at autopsy, this hypothesis does not appear to be substantiated. Moreover, the histologic picture in this case was quite unlike that which I [16d] have noted in several cases of cardiospasm, in which the involvement of the nerve tissue was unmistakable and widespread, thereby confirming the observations of Rake [16b] and of Cameron [16c] concerning the histopathologic changes found in cardiospasm. Moreover, it seems superfluous to predicate spasm or achalasia as an explanation of the difficulty in swallowing in the so-called Plummer-Vinson syndrome, when a definite cause for obstruction, namely, webs, bands or raised folds of mucous membrane, is so often apparent.

The conception of the nature of the obstruction held by Hill [18] is of interest. This writer pointed out that there is no true sphincter at the upper end of the esophagus, there being no aggregation of circular fibers. What he considered occurs in this condition is not an active contraction, obstructive or otherwise, but a passive or feebly active condition of the musculature concerned in the pharyngeal part of the

16. (*a*) Rake, G. W.: Guy's Hosp. Rep. **76**:145, 1926; (*b*) ibid. **77**:141, 1927. (*c*) Cameron, M.: J. Laryng. & Otol. **43**:219, 1928. (*d*) Suzman, M. M.: Unpublished data (paper read before the Newcastle-upon-Tyne Pathological Club, Feb. 21, 1929).

17. Cameron, M.: Brit. M. J. **1**:521, 1928.

18. Hill, W.: Brit. M. J. **1**:467, 1928.

act of deglutition. In other words, the interference with swallowing is of the nature of a muscular paresis together with reduced sensibility of the mucosa, rather than hyperesthesia and increased reflex contraction. Swallowing is impeded owing to feeble effort and the fact that the pharyngo-esophageal junction is not well opened up on account of impaired reflex stimulus. Hill is of the opinion that the atrophic lesion in the lower part of the pharynx in these feeble anemic patients is in many respects similar to that observed in patients with chronic nasal catarrh, whose palate is thinned, shrunken and almost immobile and who show atrophy of the glands, mucosa and muscles. This conception of the nature of the pharyngo-esophageal condition is of interest in view of the fact that, in the case coming to autopsy, atrophic changes were noted not only in the mucosa but also in the muscle tissue of this region.

The view of Evans,[10] that the underlying cause of the lesions of the mouth, tongue, pharynx and esophagus is syphilis, is not substantiated by the histologic observations, either at these sites or in the tissues of the other organs. Moreover, the histologic evidence that these lesions are truly inflammatory is scanty, since the chief findings were those of hyperkeratinization of the epithelium, with areas of desquamation, and an atrophic degeneration of the underlying muscle tissue. This is of importance since these lesions have usually been regarded by most writers as inflammatory and are referred to as "glossitis" and "esophagitis." It will be recalled that Hurst [6] and Ryle [7] considered the condition of the tongue as a streptococcal glossitis.

The relationship between the anemia and the dysphagia has always been a subject of contention. It has usually been held that the dysphagia is the primary disease, and that the anemia is secondary, developing as a result of the consequent unbalanced and restricted diet. To support this view, it has been put forward that the anemia usually develops in patients who have suffered from dysphagia for years. Witts,[11] however, has remarked on the fallacy of placing too much reliance on the sequence of events, pointing out that, whereas dysphagia is usually an alarming symptom, anemia and glossitis may easily pass unnoticed. Moreover, that the anemia may precede the onset of the dysphagia, even by many years, has been reported by several writers,[19] and was obvious in my case 5.

Another reason usually cited as evidence of the dependence of the anemia on the dysphagia is that, following the relief of the latter by means of instrumentation, improvement in the condition of the blood

19. (*a*) Moersch and Conner.[5] (*b*) Hurst.[6] (*c*) Cameron.[9] (*d*) Witts.[11] (*e*) Davies, D. T.: Lancet **2**:385, 1931.

is said usually to take place. It should be borne in mind, however, that, in addition to the passage of bougies, treatment usually consisted also of the administration of iron and arsenic. In this connection, the observations of Johnson [20] are of importance. This investigator pointed out that after the passage of bougies, although dysphagia ceased, the rise in the hemoglobin concentration, if it occurred at all, was extremely slow, taking in some cases a period of eighteen months to return to normal figures, whereas he obtained improvement in the condition of the blood after the administration of liver extract and of large doses of iron. It seems, therefore, from these considerations, that the contention that the development of anemia is dependent on the dysphagia cannot be upheld.

That the esophageal lesions and the consequent difficulty in swallowing are probably the result of an extension to the pharyngo-esophageal region of the lesions of the mouth and tongue is demonstrated by the fact that the latter may exist for a considerable time before the onset of the dysphagia,[21] and that they are usually present when the dysphagia is first noticed.[22] Further evidence to support this view is the apparent histologic identity of the lesions of the tongue and of the pharyngo-esophageal region (case 8).

Except for the dysphagia, all the manifestations of this syndrome, including the response to iron therapy, are indistinguishable from those of idiopathic hypochromic anemia,[23] also described under various other terms, such as achylic chloranemia,[24] idiopathic secondary anemia,[25] chronic hypochromic anemia [26] and simple achlorhydric anemia.[27]

The dysphagia, it seems, is merely a complication or concomitant manifestation of this already well recognized form of anemia, and there does not appear to be sufficient reason to regard this so-called "Plummer-Vinson syndrome" as a separate clinical entity. From an etiologic standpoint, therefore, this syndrome may be considered simply one that may arise in "idiopathic hypochromic anemia."

Since the administration of large amounts of iron almost invariably relieves the anemia and usually alleviates the lesions of the tongue and

---

20. Johnson, R. S.: Proc. Roy. Soc. Med. (Sect. Laryng.) **24**:1206, 1931.

21. Davies.[19e] Case 5 of present series.

22. Paterson.[12] Davies.[19e]

23. Mills, E. S.: Canad. M. A. J. **22**:175, 1930. Minot, G. R., and Health, C. W.: Am. J. M. Sc. **183**:110, 1932.

24. Kaznelson, P.; Reimann, F., and Weiner, W.: Klin. Wchnschr. **8**:1071, 1929.

25. Watkins, C. H.: A Classification of Chronic Idiopathic Secondary Anemia, J. A. M. A. **93**:1365 (Nov. 2) 1929.

26. Altschuller, G.: Acta med. Scandinav. **70**:119, 1929.

27. (*a*) Davies.[19e] (*b*) Witts, L. J.: Guy's Hosp. Rep. **80**:253, 1930. (*c*) Davies, D. T.: Quart. J. Med. **24**:447, 1931.

mouth, a virtual deficiency of this metal may play some part in the etiology of this disease, be it a lack of supply, a failure of absorption or an inability to utilize the metal. In view of the recent work concerning the rôle of the stomach in the etiology of anemia,[28] it is not improbable that the underlying cause of idiopathic hypochromic anemia and thus of the syndrome, glossitis, dysphagia and anemia, is in the nature of a deficiency dependent on a gastric abnormality.

SUMMARY

1. In addition to a short review of the literature, the reports of eight cases of the syndrome of anemia, glossitis and dysphagia (the so-called "Plummer-Vinson" syndrome) are presented, together with the observations at autopsy in one instance.

2. Throughout the tongue, hypopharynx and esophagus, microscopic examination disclosed a condition of hyperkeratinization of the epithelium with areas of desquamation and an atrophic degeneration of the underlying muscle tissue. The intermuscular nerve plexus (Auerbach) revealed no abnormality. The condition did not appear to be inflammatory.

3. A discussion of the etiology of this syndrome and of its relationship to "idiopathic hypochromic anemia" is presented.

Dr. James H. Means granted permission to use the cases in the medical services and outpatient departments of the Massachusetts General Hospital for this study.

28. Davies (footnotes 19e and 27c). Mettier, S. R., and Minot, G. R.: Am. J. M. Sc. **181**:25, 1931. Castle, W. B.: ibid. **178**:748, 1929. Castle, W. B., and Townsend, W. C.: ibid. **178**:164, 1929. Castle, W. B.; Townsend, W. C., and Heath, C. W.: ibid. **180**:305, 1930. Castle, W. B.: Heath, C. W., and Strauss, M. B.: ibid. **182**:741, 1931.

BLOOD CHOLESTEROL IN THYROID DISEASE

I. ANALYSIS OF FINDINGS IN TOXIC AND IN NONTOXIC GOITER BEFORE TREATMENT

LEWIS M. HURXTHAL, M.D.
BOSTON

In December, 1930, Mason, Hunt and I [1] published observations on the blood cholesterol in hyperthyroidism and hypothyroidism. The results of forty-seven determinations of the blood cholesterol in patients with toxic goiter were reported, and it was definitely shown that low values were found in severe cases, although there appeared to be no individual reciprocal relationship between the elevation of the basal metabolic rate and the lowering of the blood cholesterol. The present study was begun on a larger group of patients to determine whether our impression that the degree of clinical toxicity is reflected more accurately in the lowering of the blood cholesterol than by the basal metabolic rate is correct. Furthermore, the behavior of the blood cholesterol as the result of the various therapeutic procedures warranted further study.

METHOD OF STUDY

The cases studied were unselected, specimens of the blood having been taken as a routine in all cases of goiter. Thus the series is practically consecutive. In all of the cases in this group a metabolism test was made on the morning after admission to the hospital (unless the patient was too ill). Following this procedure, specimens of the blood were taken before the patient was given breakfast. While the blood cholesterol is not appreciably affected if the determination is made shortly after a meal, it was considered desirable to obtain the blood under uniform conditions. With rare exceptions, all specimens of blood were taken in this manner.

Analysis of the plasma was made by the method of Bloor, Pelkan and Allen,[2] under the supervision of Miss Hazel M. Hunt, director of the laboratories at the New England Deaconess Hospital. Duplicate

From the Medical Department of the Lahey Clinic and the Chemical Laboratories of the New England Deaconess Hospital.

1. Mason, R. L.; Hunt, H. M., and Hurxthal, L. M.: Blood Cholesterol Values in Hyperthyroidism and Hypothyroidsim: Their Significance, New England J. Med. **203**:1273 (Dec. 25) 1930.

2. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: J. Biol. Chem. **52**:191 (May) 1922.

analyses were made on all specimens. With the technic employed in this laboratory, the probable error does not exceed 5 per cent (over 1,700 separate specimens of blood were analyzed in this study alone). Hemolysis was encountered occasionally, but this does not appear to affect the result. All specimens were separated from the plasma on the same day, and were precipitated and analyzed when time permitted.

EXOPHTHALMIC GOITER

Effect of Previous Administration of Iodine.—The blood cholesterol was determined in two hundred and eighty-three patients with exophthalmic goiter on their admission to the hospital. These cases were divided into three groups as follows: (1) those in which some form of iodine had apparently been given before the patients came under observation; (2) those in which it was stated that the patients had received

TABLE 1.—*Exophthalmic Goiter: Average Cholesterol on Admission to Hospital in 283 Cases Grouped According to the History of Taking Iodine Previously* *

Groups	Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight	Number of Cases
Iodine taken before admission...	134	+42	103	126	— 8	129
Indefinite history regarding iodine	133	+47	110	125	— 9	30
No history of having taken iodine	127	+48	109	118	—11	124
Total of three groups						283

* Fractions are omitted, the nearest integral being chosen.

no form of iodine, and (3) those in which the question of the administration of iodine could not be answered. The average of these findings is shown in table 1. (Tables showing individual analyses will be published in a separate article on the effect of treatment.) It is interesting to note that the average cholesterol value in each group differs in about the same magnitude as the metabolism, pulse rate and weight.

The Numerical Distribution of Cholesterol Values in Exophthalmic Goiter.—The lowest value found for those patients who gave no history of receiving iodine before coming under our care was 53 mg. per hundred cubic centimeters. The highest figure found was 245 mg. The smoothed frequency curves are seen in chart 1. The shift of the curve to the left of that produced by the values found in nontoxic goiter is evident.

Comparison of Average Cholesterol Values with Average Deviation from Normal Weight and History of Weight Lost.—Those cases in which there was no history of the patient's having taken iodine were

used for this analysis. This tabulation is to be seen in tables 2 and 3. In a general way, the average cholesterol values decrease slightly in the groups which lost the greatest weight, but the difference is not so striking as will be found in comparison of the average observed values in severe hyperthyroidism and those in auricular fibrillation with or without congestive heart failure. There is no significant difference in the groups that showed deviation from normal weight. This is what might be expected, because a person who is usually underweight might have mild hyperthyroidism while an obese patient might be extremely ill.

Comparison of Average Cholesterol Values by Age Groups.—In table 4 the values in one hundred and twenty-four cases in which the patients received no iodine are arranged according to decades. The averages show no significant change with age.

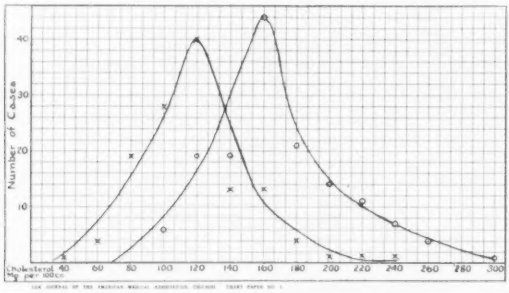


Chart 1.—Smoothed frequency curves of cholesterol values in untreated exophthalmic goiter (cross line) and nontoxic goiter (circle line).

Severe Hyperthyroidism, Auricular Fibrillation and Congestive Heart Failure.—Of interest are the findings in this group of patients. Twenty-four patients with exophthalmic goiter were admitted with auricular fibrillation, sixteen of whom had congestive heart failure (table 5). It is obvious that congestive heart failure is not responsible for the low cholesterol values in view of the low values found in other cases (table 6). This observation is further borne out by the fact that in ten cases of congestive heart failure not associated with goiter in which specimens of the blood were obtained, the average value was 162 mg. per hundred cubic centimeters.

While auricular fibrillation occurs frequently in patients who are obviously severely toxic, it is frequently seen in subjects who at first glance appear only slightly activated. The latter fall into a group which Dr. Lahey has termed "the apathetic type." The low cholesterol would seem to indicate that auricular fibrillation is associated with the severity of hyperthyroidism, an accurate estimation of which cannot be arrived at from the basal metabolic rate alone. However, the low cholesterol

values in these cases are associated in a general way with the higher basal metabolic rates (table 5).

In table 6 are listed values in the severely ill patients without auricular fibrillation or congestive heart failure. The patients in this

TABLE 2.—*Exophthalmic Goiter: Average Blood Cholesterol Correlated with Deviation from Normal Weight for Patients Not Receiving Iodine Before Admission*

Groups	Cholesterol, Mg. per 100 Cc.	Average Percentage Deviation from Normal Weight	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Number of Cases
30 per cent or more underweight	128	—37	+52	102	128	10
20-29 per cent underweight	127	—25	+48	113	104	23
10-19 per cent underweight	125	—14	+51	107	112	36
1- 9 per cent underweight	121	— 6	+41	110	127	25
Normal weight or over	127	+ 6	+49	109	141	30

TABLE 3.—*Exophthalmic Goiter: Correlation of Average Blood Cholesterol with Average Loss of Weight in Patients Not Receiving Iodine Before Admission* *

Groups	Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight	Number of Cases
No loss	137	+44	109	122	— 5	12
1- 9 pounds loss	130	+49	112	108	—14	20
10-19 pounds loss	126	+49	107	114	—13	48
20-29 pounds loss	118	+46	100	119	— 3	12
30-39 pounds loss	122	+50	104	121	—11	14
40-49 pounds loss	123	+49	121	123	— 5	8
50 pounds or over	120	+52	95	120	—27	4

* Loss of weight not recorded in six.

TABLE 4.—*Exophthalmic Goiter: Average Cholesterol Values by Decades for Patients Not Receiving Iodine Before Admission*

Age Groups	Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Weight in Pounds	Number of Cases
10-19 years inclusive	113	+49	101	7
20-29 years inclusive	128	+47	119	33
30-39 years inclusive	127	+48	115	38
40-49 years inclusive	113	+48	122	29
50-59 years inclusive	108	+46	108	10
60-69 years inclusive	131	+49	131	7

group were in the so-called thyroid crisis or on the verge of it when they entered the hospital. The low cholesterol values are to be noted.

There were twenty-nine other patients in this series of cases who showed cholesterol values below 100 mg. on admission. Fourteen of this group, or nearly one-half, had two-stage operations. Because in only 20 per cent of our cases were multiple stage operations per-

formed and since the decision to perform one or two operations was arrived at without knowledge of the cholesterol determination, the low values were in harmony with the estimate of operative risk, which is,

TABLE 5.—*Exophthalmic Goiter: Blood Cholesterol in Exophthalmic Goiter with Auricular Fibrillation With and Without Congestive Heart Failure*

Number	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Percentage of Deviation from Normal Weight	Congestive Heart Failure	Compound Tincture of Iodine Before Admission
23638	53	+ 78	132	109	−14	+	0
20926	75*	+ 72	126	122	−10	+	0
21775	77*	+ 84	136	114	−13	+	0
4343	78*	+ 68	148	139	+ 5	+	0
24212	80*	+ 52	108	138	+ 1	+	0
6432	82*	+ 62	92	146	− 5	+	0
21897	82	+ 52	160	104	−22	+	0
22360	84	+ 69	108	112	−25	+	+
22221	85	+104	124	116	− 8	0	+
21025	86*	+ 41	100	77	−44	+	0
23904	93	+ 67	106	154	+10	+	0
22785	97	+ 62	120	156	−10	+	0
22947	105	+ 23	100	153	+17	0	0
23434	111	+ 26	90	120	−27	0	0
23951	118	+ 44	146	117	−12	+	+
23194	119	+ 45	92	104	−24	0	+
21752	123	+ 45	104	176	− 7	0	0
20520	123	+ 51	124	150	± 0	0	0
20641	128	+ 65	100	138	−24	0	+
23268	134	+ 41	130	72	−36	+	0
24238	151	+ 20	92	113	−24	0	0
21916	154	+ 25	62	165	+17	+	+
23288	162†	+ 32	102	81	−40	+	+
21339	199	+ 69	92	117	−25	+	+
Average	108	+ 54	112	125	−13		

* Recurrent cases.
† Basal metabolism test made a few days later.

TABLE 6.—*Exophthalmic Goiter: Blood Cholesterol in Severe Exophthalmic Goiter in Crisis or on Verge of Crisis*

Number	Blood Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Percentage of Deviation from Normal Weight
24268	48*	+46	110	90	−41
21188	68*	+57	110	135	−26
20864	71	+74	142	168	+15
21936	81	+38	120	128	− 5
23594	83	+69	112	86	−43
21267	85	+74	118	151	+17
21253	95	+83	132	102	−19
22890	104	+58	100	104	−18
22548	90	+65	108	150	− 3
Average	82	+66	117	124	−15

* Basal metabolism test made a few days later.

broadly speaking, the severity of thyroid intoxication. Doubtless the decision to perform only one operation in some of these cases was made after marked improvement on the usual preoperative regimen.

Analysis of Cholesterol Values Over 180 Mg. in Exophthalmic Goiter.—Only twenty-two patients were in this group (table 7). Thir-

teen had received iodine before admission, and five were considered to be in a state of remission due to iodine. Pathologic examination showed that chronic thyroiditis was present in two. Only six were known to have received iodine, and of these three showed a cholesterol value of over 180 mg. This represents 2.4 per cent of patients seen who had not received iodine and about 1 per cent of the total number of cases of exophthalmic goiter in which determinations were made on the first day in the hospital.

TABLE 7.—*Exophthalmic Goiter: Cases Showing Cholesterol Over 180 Mg. per 100 Cc. on Admission to Hospital*

Case	Sex	Age	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Cholesterol, Mg. per 100 Cc.	Deviation from Normal Weight	Compound Tincture of Iodine Before Entering	Comment
25697	M	48	+10	84	182	197	+ 9	++	Iodine remission
24892	F	43	+ 6	96	125	233	—11	++	Iodine remission
23022	F	35	+ 4	80	130	202	— 8	++	Iodine remission
23073	F	44	+13	82	153	260	+12	++	Iodine remission
23308	F	43	+45	130	165	187	+18		
20986	F	50	+19	112	113	185	—20	0	Thyroiditis, exophthalmos
24890	F	60	+24	106	131	191	— 2	++	
21978	F	28	+34	108	137	186	0	0	Active tuberculosis
22481	F	60	0	86	103	245	—27	0	Spontaneous remission; moderate strumitis
23098	F	55	+24	88	134	219	0	?	Angina
25185	F	61	+18	90	121	184	—12	++	Iodine remission
22746	M	40	+12	110	144	272	+ 2	++	Iodine remission
21886	M	36	+60	102	112	182	—26	0	
15767	F	44	+30	108	130	198	— 8	++	Recurrent
23376	F	49	+52	100	122	186	—13	?	
22958	F	28	+38	98	158	190	+21	++	
24890	F	60	+24	106	131	191	— 3	++	
22840	F	33	+24	102	112	185	—10	0	
21339	F	50	+69	92	117	190	—25	++	
20761	F	37	+28	112	129	219	—13	++	
22731	F	30	+44	100	123	182	0	0	No loss of weight
23037	F	48	+27	78	116	213	—17	++	

TABLE 8.—*Exophthalmic Goiter: Recurrent Hyperthyroidism; Average Cholesterol Determinations in Thirty-Two Cases*

Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal Weight
127	+38	103	130	—7

Recurrent Hyperthyroidism.—Table 8 lists cases of recurrent or persistent hyperthyroidism. No separate analysis was made in these cases. Most of the patients had taken compound solution of iodine. Six other recurrent cases are listed under the group with auricular fibrillation. Attention should be called to the fact that these six patients had congestive heart failure as well and had not received compound solution of iodine. The highest cholesterol value found in these six cases of recurrent hyperthyroidism with auricular fibrillation and congestive heart failure was 82 mg. per hundred cubic centimeters.

Toxic Adenomatous Goiter.—Sixty-three cases of toxic adenomatous goiter were studied. They were grouped according to whether or not the patients had received iodine before admission (table 9). It is noteworthy that while the average cholesterol values are below the normal range, there is no evident relationship between the basal metabolic rate, pulse rate and weight, such as is shown in the group of cases of exophthalmic goiter. That iodine does not produce such changes should not be inferred from such an analysis, in view of the relative inaccuracy of such a history and the smaller number of cases.

TABLE 9.—*Toxic Adenomatous Goiter: Average Cholesterol Values on Admission to Hospital in Cases Grouped According to History of Taking Iodine Previously*

Group	Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage of Deviation from Normal Weight	Number of Cases
Iodine taken before admission....	142	+38	106	119	—11	15
Indefinite history regarding iodine	149	+30	96	131	—17	27
No history of having taken iodine	140	+40	107	129	— 7	21

TABLE 10.—*Toxic Adenomatous Goiter: Auricular Fibrillation in Toxic Adenomatous Goiter*

Sex	Age	Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Deviation from Normal Weight	Congestive Heart Failure	Iodine Before Entry
F	42	71	+61	118	129	— 7	+	+
F	65	156*	+65	72	115	—22	0	+
F	50	94	+42	98	138	— 2	+	?
F	34	88	+37	150	107	—15	0	0
F	53	179†	+16	108	138	0	0	+
F	58	125	+30	118	155	+13	+	?
F	58	147	+35	120	119	—14	0	+
F	65	99	+33	80	108	—21	+	+
F	62	88	+44	76	112	—13	+	0
Average	54	116	+40	104	125	— 9	5	—

* Long preparation elsewhere.
† Borderline toxicity.

Five cases showed a cholesterol value below 100 mg. per hundred cubic centimeters. All of the patients had auricular fibrillation; four of the five had congestive heart failure. I believe that this is significant and corresponds to the same type of case in exophthalmic goiter. The values for the patients with auricular fibrillation are shown in table 10.

NONTOXIC GOITER

One hundred and forty-six patients with nontoxic nodular goiter were examined. Of this group ninety-six showed single nodules, while fifty displayed multiple nodules. These should serve as a control for

toxic cases, except that higher values might be expected at times if the theory that some nodules form in response to a deficient secretion from other parts of the thyroid gland is true. One patient in the group showed myxedema; following the use of thyroid extract, not only did all signs of myxedema disappear, but the goiter was reduced greatly in

TABLE 11.—*Nontoxic Goiter: Average Cholesterol Values Correlated with Decades*

Age Group	Average Basal Metabolic Rate, per Cent	Average Cholesterol, Mg. per 100 Cc.	Average Pulse Rate	Average Weight in Pounds	Average Percentage Deviation from Normal
		Single Nodules			
15-29	0	162	82	133	+4
30-39	0	169	77	134	0
40-49	+3	182	83	143	+2
50-59	+4	169	87	141	0
60-69	0	224	82	144	−6
Average	+1	178	82	139	
		Multiple Nodules			
18-29	0	158	84	124	−2
30-39	+2	166	83	138	−3
40-49	+3	187	82	145	+3
50-59	0	192	82	143	+1
60-69	+7	207	86	142	−2
Average	+3	184	84	139	
Average both groups	+2	180	83	139	

TABLE 12.—*Nontoxic Goiter: Average Values Correlated with Deviation from Normal Weight*

Deviation from Normal, per Cent	Average Cholesterol, Mg. per 100 Cc.	Average Basal Metabolic Rate, per Cent	Average Pulse Rate	Average Weight in Pounds	Average Percentage of Deviation from Normal Weight	Number of Cases
		Single Nodules				
−20 down	183	+ 7	80	106	−28	9
−20 to −10	194	+ 3	81	104	−15	9
−10 to +10	171	+ 1	81	136	0	51
+10 to +20	164	0	79	157	+16	13
+20 up	181	+ 2	80	179	+34	8
		Multiple Nodules				
−20	165	+22	90	110	−25	5
−20 to −10	175	+ 1	91	120	−11	8
−10 to +10	188	+ 1	83	138	0	26
+10 to +20	192	+ 3	82	165	+19	5
+20 up	196	+ 2	76	179	+30	6

size. (The patient now wears a number 15 collar, whereas he formerly used number 17.)

The wide "scatter" of the values as seen in chart 1 certainly appears to be greater than would be expected in a group of normal persons. Correlation of average cholesterol values with age groups (table 11) suggests strongly that higher levels are found as age advances. The results found on correlating cholesterol values with deviation from normal weight are not striking (table 12). Not a few of the patients

TABLE 13.—*Chronic Thyroiditis*

Sex	Age	Cholesterol, Mg. per 100 Cc.	Basal Metabolic Rate, per Cent	Pulse Rate	Weight in Pounds	Deviation from Normal Weight	Operated	Comment
F	58	255	— 1	90	109	—23	+	
F	52	240	+20	82	107	—19	+	
F	42	191	—15	72	127	—13	+	
F	59	223	— 6	84	147	+ 4	+	
F	46	159	—11	76	140	— 1	+	
F	58	189	+15	80	113	—21	+	
F	43	227	+ 4	80	157	+15	0	
F	51	252	— 1	86	108	—27	0	
F	49	181	—18	82	152	0	0	
F	67	236	+ 5	78	135	— 2	0	
F	19	167	+ 4	88	116	— 8	0	
F	..	191	—14	..	...	....	0	Basal metabolism test performed elsewhere
F	51	240	—20	68	141	—10	0	
F	53	244	— 9	62	125	— 7	0	Mild myxedema
F	49	227	— 8	66	134	— 2	0	
F	52	208	—15	72	149	+10	0	
F	46	240	—27	68	125	—20	+	Operation 4 months before for drainage of abscess of thyroid; mild myxedema developed
Average.....		216	— 6	77	130	— 8	7	

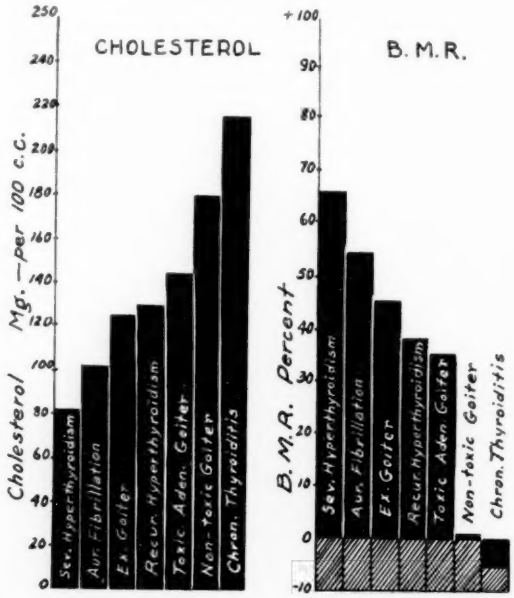


Chart 2.—Average cholesterol values and average basal metabolic rates in the various clinical groups of patients with goiter. The group labeled severe hyperthyroidism includes cases of exophthalmic goiter and toxic adenomatous goiter. The group labeled auricular fibrillation includes all those with exophthalmic goiter, recurrent exophthalmic goiter and toxic adenomatous goiter. In the group labeled exophthalmic goiter are placed all cases of exophthalmic goiter, including those with auricular fibrillation or in thyroid crises. Recurrent hyperthyroidism designates recurrent exophthalmic goiter.

showing blood cholesterol values of over 220 mg. per hundred cubic centimeters showed evidence of marked vascular disease. Further analysis of this group will be presented in a later paper.

CHRONIC THYROIDITIS

Some cases of myxedema are clearly caused by chronic thyroiditis, the most severe form of which is Riedel's struma. Fifteen such cases were encountered, in seven of which operation for tracheal pressure was performed and the diagnosis thus established. Two of the fifteen patients showed mild myxedema, and operation was not performed. Subsequent thyroid therapy has relieved these two patients.

Certainly, if there is a borderline state between normal thyroid function and nonevident clinical hypothyroidism, it should be produced by this type of thyroid disease. The cholesterol values found in this group are listed in table 13.

COMMENT

The purpose of this paper is to present values obtained for blood cholesterol in toxic and in nontoxic goiter before treatment. References to the literature have been listed elsewhere.[1] Subsequent papers appearing since then will be referred to in the subsequent reports of this study, which will deal with the results of treatment and with further observations in myxedema and other clinical conditions.

In chart 2, the average values of the toxic and nontoxic groups are shown graphically along with the average metabolic rates in those groups. Scrutiny of this chart clearly demonstrates the general reciprocal relationship between the mean cholesterol values and the mean basal metabolic rates. If the mean values for cholesterol and the basal metabolic rate in myxedema as reported from this laboratory [1] were added to this chart, a still more striking relationship would be seen (average cholesterol, 336 mg. per hundred cubic centimeters; average basal metabolic rate, minus 33 per cent—twenty-three cases).

SUMMARY AND CONCLUSION

1. The blood cholesterol during fasting was determined as a routine in five hundred and five cases of thyroid disease, along with the pulse, the weight and the basal metabolic rate.

2. The lowest average values for blood cholesterol are found in patients in or near thyroid crises.

3. Auricular fibrillation in toxic goiter is associated with the next lowest average level of cholesterol.

4. The average cholesterol value in all types of exophthalmic goiter is lower than in toxic adenomatous goiter.

5. Recurrent hyperthyroidism is associated with cholesterol values that are almost as low as those in exophthalmic goiter.

6. The average cholesterol value in nontoxic goiter is normal, although the scatter is wider than expected. Age appears to raise the blood cholesterol in these cases.

7. Chronic thyroiditis is associated with higher average values than in any other thyroid disease except myxedema.

8. The level of the blood cholesterol and the basal metabolic rate bear a reciprocal relationship when judged by average values.

INTRAVENOUS PRESSURE

I. NEW METHOD OF DETERMINATION

W. A. BRAMS, M.D.

L. N. KATZ, M.D.

AND

W. J. SCHUTZ, M.D.

CHICAGO

Intravenous pressure may be estimated clinically by either direct or indirect methods. The former is accomplished by the use of a hollow needle or trocar inserted into a vein and connected with a suitable manometer, while the indirect methods are based on the principle of measuring the external pressure necessary to obliterate the vein so that it is no longer visible above the surface of the skin.

Determination of intravenous pressure by direct methods has been described by Moritz and von Tabora,[1] Schott,[2] Bedford and Wright[3] and others. Such direct methods, while more accurate, have certain disadvantages which preclude their general use in clinical medicine. The more important objections are the impossibility of frequent determinations in the same patient, the necessary prerequisite of strict asepsis, the possibility of formation of clot in the needle, which interferes with accurate readings and the difficulty sometimes encountered in puncturing a vein obscured by fatty tissue in obese persons. We have also had apprehensive patients who could not rest quietly or who became frightened by the venous puncture, with the result that the venous pressure was elevated considerably.

The indirect or bloodless methods are free from most of these objections, but the prevailing procedures are attended by other disadvantages which prevent their adoption for universal use in routine examination of patients. Attempts have been made to overcome some of the disadvantages inherent in such methods by Frey,[4] von Basch,[5]

From the Heart Station, Michael Reese Hospital, and the Department of Physiology, Northwestern University Medical School.

This research was aided by the Emil and Fanny Wedeles Fund of the Michael Reese Hospital for the Study of Diseases of the Heart and Circulation.

1. Moritz and von Tabora: Deutsches Arch. f. klin. Med. **98**:475, 1910.
2. Schott, E.: Deutsches Arch. f. klin. Med. **108**:537, 1912.
3. Bedford, D. E., and Wright, S.: Lancet **2**:106, 1924.
4. Frey, A.: Deutsches Arch. f. klin. Med. **73**:511, 1902.
5. von Basch, S.: Arch. di sc. biol. **2**:117, 1904-1905.

Hooker,[6] Eyster [7] and others, but certain objections still remain, the most serious being that the end-point is not sharp, and that correct estimations are therefore difficult to obtain unless they are made by those who are expert with the particular device used. Another important disadvantage is the impossibility of applying such methods to obese persons in whom the veins are not visible above the surface of the skin. Indirect methods are still further limited by certain possibilities for error because of inherent defects in the construction of the apparatus or by the fact that the end-point must be determined quickly.

It is not our purpose to give a detailed review of the methods now in use, because our procedure is based on a new principle. We believe that the method to be described eliminates most of the objections mentioned, and that it has the additional advantage of a sharp end-point which can be read without hurry.

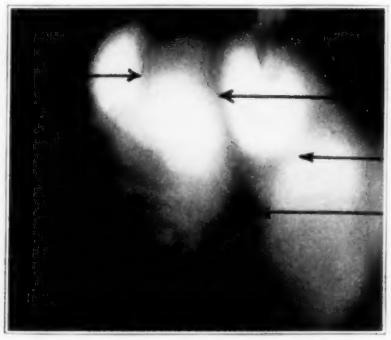


Fig. 1.—Appearance of veins on transillumination, indicated by arrows.

As in other indirect methods, it is necessary to proceed under basal conditions, which consist of placing the patient at rest for ten minutes in a horizontal or semirecumbent position. The arm and hand to be examined are supported horizontally by a pillow and held at a level which corresponds to the point of entrance of the vena cava into the right auricle. Following the suggestion of Eyster, we estimate this point to be in the fourth interspace, at the junction of the anterior and middle third of the anteroposterior diameter of the thorax. This furnishes a fixed point for estimating the venous pressure, so that future determinations can be compared, and gives, in addition, the pressure at the level at which the veins enter the heart.

6. Hooker, D. R., and Eyster, J. A. E.: Bull. Johns Hopkins Hosp. **19**:274, 1908.

7. Eyster, J. A. E.: The Clinical Aspects of Venous Pressure, New York, The Macmillan Company, 1929.

The method itself is based on the principle that the superficial veins on the dorsum of the hand can be easily visualized in a darkened room by placing a small light, such as an ordinary pocket flashlight, against the palmar surface, preferably in the interosseous spaces.[8] The superficial veins by this transillumination appear as black bands which can be obliterated by moderate pressure, and thus distinguished from shadows cast by ligaments.

The mouth of a small glass funnel is covered by a thin rubber dam held securely in place by a thread tied tightly in a previously pre-

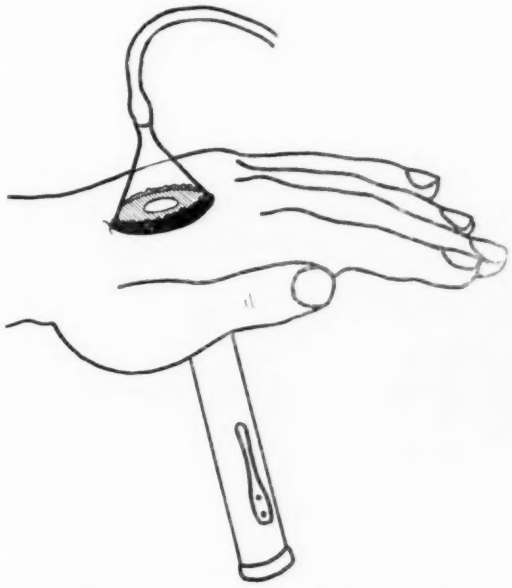


Fig. 2.—Diagram of arrangement used for new method of measuring venous pressure.

pared groove near the rim. A small hole is then cut in the center of the rubber dam, through which the vein to be examined is visualized. Such a vein is previously selected in a darkened room in the manner indicated, and its location marked. The surface of the rubber dam is then covered with rubber cement, and the funnel is placed on the dorsum of the hand so that the previously selected vein is seen through the aperture in the rubber. The funnel is held in place by moderate

8. This was suggested by observing the appearance of the veins during transillumination of a breast by Dr. Max Cutler.

pressure until the rubber is adherent to the skin. This makes an air-tight seal. The tip of the funnel is then connected by rubber tubing to a suitable water manometer which is so graduated that pressure may be read in millimeters of water. The room is again darkened, or a black cloth is placed over the head of the observer, and the light is placed against the palmar surface of the hand in order to visualize the dorsal vein within the aperture of the rubber dam. The air pressure is then slowly raised in the instrument by a suitable rubber bulb—with the leak-valve shut—until the vein under examination becomes obliterated as a result of the external compression. It is important to distinguish two stages; the first is the obliteration of the vein, and the second, further blanching of the skin. We have selected the former as the end-point at which the pressure is read off in the manometer in millimeters of water. A diagram of the set-up is shown in figure 1,

Venous Pressure

Name	Diagnosis	Direct Reading (Mm. H_2O)	Indirect Reading (Mm. H_2O)
H. S.	Rheumatism; mitral stenosis and insufficiency; moderate decompensation	135	135
I. R.	Normal	55–60	50
B. P.	Noncardiac	70	75–80
A. C.	Noncardiac	65	65
K.	Hypertensive heart disease; compensated	45	40–45
S. P.	Noncardiac	65	60–65
C. M.	Noncardiac	60	70–75
W. L.	Noncardiac	90	105
J. L.	Noncardiac	60	60
A. S.	Hypertensive heart disease; moderate decompensation	110	115
G. D.	Noncardiac	85	85–90
R. G.	Hypertensive heart disease; obesity; slight decompensation	100	90

and a photograph of the appearance of the veins on transillumination is shown in figure 2.

We were careful to avoid error by covering the head of the observer with a black cloth, while another person noted the height of the water column in the manometer tube. Several readings were taken for each patient, and the end-point was announced by signal to the person reading the manometer. A series of twelve patients were examined by this procedure, and the results were later compared with those obtained by the direct method (table).[9] These patients consisted of persons with cardiac disease and a group suffering from other than cardiac disease. An obese patient whose veins were not visible above the surface of the skin and who could not be examined by the Eyster method is included in this series. The device has also been tried in

9. The apparatus for this has been described elsewhere. (Katz, L. N.; Hamburger, W. W., and Rubinfeld, S. H.: Observations on Oxygen Therapy: II. Changes in the Respiration and Circulation, Am. J. M. Sc. **184**:810 [Dec.] 1932.)

colored patients and has been found practicable. The table shows that a high degree of accuracy is possible when the results of our indirect method are compared with those obtained by the direct method.

We are presenting this report for the purpose of describing a new principle in the estimation of venous pressure. We believe that with minor improvements in the instrument and technic the method can be adopted for general clinical use. The advantages over other indirect methods are its greater accuracy, the simplicity of the apparatus and the possibility of its use in obese and other patients in whom other indirect or direct procedures may fail. We are projecting a series of experiments in an attempt to use this method clinically in order to determine its practicability.

TRANSIENT METHEMOGLOBINEMIA DUE TO AMMONIUM NITRATE

LEONARD TARR, M.D.
NEW YORK

Toxic manifestations due to the administration of large doses of the nitrates are well known. This is particularly true of bismuth subnitrate.[1] The most striking finding in such patients is methemoglobinemia with severe cyanosis. The factor responsible is a reduction of the nitrate to the nitrite with subsequent transformation of the hemoglobin to methemoglobin.

In 1926 Jacobs and Keith [2] suggested the use of ammonium nitrate as the least disagreeable and the most effective of the acid-producing salts to be used as a diuretic. They employed it extensively at the Mayo Clinic without any detrimental effects.

In 1928 Barker and O'Hare [3] reported for the first time the appearance of severe cyanosis in a patient with nephrosis who had received 15 Gm. of ammonium nitrate a day for ten days. They attributed the condition to methemoglobinemia, although spectroscopic examination of the blood was not made.

In 1929 Eusterman and Keith [4] reported the occurrence of transient methemoglobinemia in two patients who had received ammonium nitrate. Their first case was in a man 32 years of age with edema of renal origin complicating a gastro-enterostomy that did not function properly. He suffered from severe gastric and intestinal distress. Following the administration of 54 Gm. of ammonium nitrate during a period of ten days, marked cyanosis developed which was shown spectroscopically to be due to methemoglobinemia. In addition, the patient was very weak and irrational and fainted once. When the drug was discontinued he returned to his previous condition within forty-eight hours. The second patient was a woman, 47 years of age, with marked edema and ascites, probably secondary to syphilitic cirrhosis of the liver, who suf-

From the Medical Division of the Montefiore Hospital.

This work was done under the auspices of the Hilda Stich Stroock Fellowship.

1. Beck, E. G.: Toxic Effects from Bismuth Subnitrate, J. A. M. A. **52**:14 (Jan. 2) 1909.

2. Jacobs, M. F., and Keith, N. M.: The Use of Diuretics in Cardiac Edema, M. Clin. North America **10**:605 (Nov.) 1926.

3. Barker, M. H., and O'Hare, J. P.: The Use of Salyrgan in Edema, J. A. M. A. **91**:2060 (Dec. 29) 1928.

4. Eusterman, G. B., and Keith, N. M.: Transient Methemoglobinemia Following Administration of Ammonium Nitrate, M. Clin. North America **12**:1489 (May) 1929.

fered from severe constipation as well. On two occasions cyanosis due to methemoglobinemia developed, once after a total of 24 Gm. given 10 Gm. a day, and again after a total of 89 Gm. given 8 Gm. a day. In normal patients and in dogs the authors were unable to produce methemoglobinemia with the drug. They regard the reduction of the nitrate to the nitrite in the bowel as an abnormal process.

In 1928 Christian,[5] in a discussion of the use of ammonium nitrate as a diuretic, mentioned the fact that he saw a patient in whom methemoglobinemia developed after the administration of the drug. He does not state the diagnosis, the predisposing factors or the amount given.

In 1930 Keith, Whelan and Bannick,[6] in a complete study of nitrate diuresis, reported another case of methemoglobinemia. Their patient suffered from chronic nephrosis and was in addition very constipated. The methemoglobinemia developed after the patient had received 10 Gm. of the drug a day for twelve days.

In all the patients the symptoms and signs cleared up rapidly after the drug was discontinued.

Since 1929 ammonium nitrate has been used as a diuretic and as an adjuvant to diuresis at the Montefiore Hospital. It is given in gelatin-coated tablets weighing 0.5 Gm. each, or as a 40 per cent aqueous solution in doses of 6 to 8 Gm. per day. Only occasionally is this dose exceeded. It has been found the least disagreeable and the most effective of the acid-producing salts. In two years of its use no toxic manifestations were seen. During this time more than 65,000 Gm. of ammonium nitrate was consumed in a medical service which has a large number of patients suffering from cardiovascular diseases. The substance has been tested for nitrites as impurities, and none were found. Recently, within a short time, in the following four patients severe cyanosis due to methemoglobinemia developed after the administration of ammonium nitrate.

REPORT OF CASES

CASE 1.—*History.*—S. B., a Russian Jew, 45 years of age, enjoyed good health until his present illness. In September, 1930, he began to complain of progressively increasing shortness of breath and noticed swelling of the lower extremities. The result of an examination of the urine for albumin was 4 plus. He entered a hospital shortly thereafter, where a diagnosis of nephrosis was made. Under high protein feeding and the administration of diuretics there was slight improvement in his condition. He was transferred to Montefiore Hospital on March 18, 1931.

Physical Examination.—The patient was a well developed, middle aged, ambulant man, complaining chiefly of weakness and swelling of the lower extremities. There was decided oxycephaly. The eyegrounds showed medullated nerve fibers, but no

5. Christian, H. A., in discussion on Keith, N. M.; Whelan, M., and Bannick, E. G.: Diuretic Action of Nitrates and Their Use in the Treatment of Dropsy, Tr. A. Am. Physicians **43**:290, 1928.

6. Keith, N. M.; Whelan, M., and Bannick, E. G.: The Action and Excretion of Nitrates, Arch. Int. Med. **46**:797 (Nov.) 1930.

other changes. The heart was slightly enlarged to the left; the rhythm was regular, and there was an accentuation of the second aortic sound. The blood pressure ranged from 124 systolic and 90 diastolic to 170 systolic and 110 diastolic. There was evidence of a right hydrothorax. Over the abdominal wall was a network of collateral circulation that was more prominent on the right side. The liver was firm and reached to the level of the umbilicus. Edema of the lower extremities was marked.

Laboratory Data.—On a limited fluid intake, he voided from 400 to 600 cc. of urine daily, which contained on an average 2.5 per cent of albumin. The specific gravity ranged up to 1.035. Hyaline and granular casts and double refractive bodies were present. The test for Bence-Jones protein was negative. Chemical examination of the blood showed a marked diminution of the serum albumin and globulin to 1.7 and 2.7 mg. per hundred cubic centimeters, respectively. The fat content increased to 2.04 mg. Later, under treatment, the serum albumin and globulin rose to 2.8 and 3.8 mg., respectively. The blood urea nitrogen and creatinine were normal. Thoracentesis of the right side of the chest on several occasions yielded a milky fluid which contained 0.5 per cent protein and 0.2 per cent fat. Inoculation of guinea-pigs with the aspirated fluid from the chest was negative for tuberculosis. The Bennhold test for amyloid disease was negative.

Diagnosis.—It was felt that the underlying condition was chronic glomerulonephritis and that the patient was in the nephrotic phase. The large liver and the collateral circulation were accepted as evidence of a lesion about the entrance of the inferior vena cava through the diaphragm, perhaps an obliterative pleurisy or a tuberculous process. Roentgen examination showed diffuse proliferative changes in this region.

On the death of the patient several months later, the true diagnosis was disclosed. There was an old thrombosis of the inferior vena cava extending into the renal veins on both sides. The lumen of the veins was completely obliterated. There was evidence of an increased collateral circulation in the perirenal tissue and in the veins of the renal capsule. The latter stripped easily and left a smooth, yellow, injected surface. The consistence was flabby, and the cut surface smooth and greasy. There was a sharp contrast between the yellow cortex and the red medulla. On microscopic section the kidneys showed diffuse fatty degeneration of the parenchymatous elements.

The right lung was reduced to about one-fourth the normal size and covered with thin sheets of fibrin. The lower lobe was partially collapsed. Between it and the diaphragm was a large encapsulated collection of soft, semitranslucent gelatinous material, not unlike the postmortem "chicken fat" clot. There was in addition a moderate amount of milky fluid. The whole lesion was apparently an old encapsulated pleurisy or empyema that had undergone extensive change.

A more complete clinical and anatomic description of this case will appear in a separate report.

Course and Treatment.—The patient was maintained with varying success on urea, occasional doses of salyrgan and ammonium nitrate in an attempt to control the edema. By Oct. 6, 1931, he had received 696 Gm. of ammonium nitrate at the rate of 6 Gm. a day almost continuously for nearly eighteen weeks. It was then decided to increase the dose to 9 Gm. a day. After two weeks of therapy with the larger dose severe cyanosis of the hands, feet and face suddenly developed. The mucous membranes had an ashen blue, almost violaceous color. The patient felt weak and complained of substernal oppression. The blood pressure was 150 systolic and 94 diastolic; the pulse rate was 90. Neurologic examination showed hyperreflexia of both the upper and the lower extremities, bilateral, inexhaustible

ankle clonus and a bilateral Babinski and a bilateral Hoffman sign in addition to numerous twitching movements of the fingers.

All medication except inhalation of oxygen was discontinued. By the next morning this dramatic picture had disappeared, and the patient was his former self. He was not given the drug again. Blood drawn at the height of the cyanosis was dark chocolate brown and did not change on shaking and exposure to the air. The urea nitrogen was 17 mg. per hundred cubic centimeters, and the carbon dioxide 50 per cent by volume. The urine showed the usual amount of albumin and double refractive bodies. The blood count showed 4,200,000 red blood cells with 75 per cent hemoglobin. Unfortunately, the blood was not examined spectroscopically for methemoglobin. The clinical picture of sudden onset and rapid disappearance of cyanosis and the chocolate brown color of the blood leave little doubt as to the diagnosis of methemoglobinemia.

Summary.—A man, 45 years old, with marked albuminuria and edema due to bilateral occlusion of the renal veins simulating clinically the picture of a lipoid nephrosis was able to tolerate 696 Gm. of ammonium nitrate given 6 Gm. a day for eighteen weeks. Following the same medication administered 9 Gm. a day severe methemoglobinemia developed in two weeks.

CASE 2.—*History.*—M. A., a Turkish Jew, 48 years of age, was admitted to Montefiore Hospital on May 29, 1931. For at least four years prior to this time he had been complaining of weakness, shortness of breath and swelling of the lower extremities. On repeated admissions to other hospitals his illness had been diagnosed as chronic glomerulonephritis.

Physical Examination.—The patient was a well developed and well nourished, but rather pale man, comfortable and ambulant. There was bilateral neuroretinitis, without much disturbance in vision. The heart was moderately enlarged to the left, showing on fluoroscopy involvement chiefly of the left venticle. The blood pressure ranged from 110 systolic and 80 diastolic to 160 systolic and 90 diastolic. The lungs were clear. No abdominal viscera were palpable. There was marked pitting edema of the lower extremities extending up to the knees.

Laboratory Data.—There was moderate polyuria with excretion of from 1,500 to 2,000 cc. in twenty-four hours. The specific gravity of the urine was fixed between 1.013 and 1.017. From 5 to 6 Gm. of albumin per liter was present. Hyaline and granular casts and red blood cells were found in the urinary sediment. Chemical examination of the blood showed a urea nitrogen of 40 mg. per hundred cubic centimeters; creatinine, 3.7 mg.; cholesterol, 250 mg.; serum albumin, 1.87 mg., and serum globulin, 3.36 mg. There was moderate secondary anemia with a count showing 2,980,000 red blood cells and 56 per cent hemoglobin (Sahli). The Bennhold test for amyloid disease showed 40 per cent retention of the dye after one hour, which is presumptive evidence of amyloidosis.

Diagnosis.—The diagnosis was: chronic glomerulonephritis with a nephrotic component, moderately severe renal insufficiency and probable amyloidosis.

Course and Treatment.—Persistent edema of the lower extremities required diuretic therapy for relief. For a time the patient was given from 40 to 60 Gm. of urea a day with beneficial results. On Oct. 21, 1931, he was given 2 Gm. of ammonium nitrate three times a day. He had never received this medication before. During the following eight days he received a total of 50 Gm. On Oct. 29, 1931, in the course of several hours severe cyanosis developed. His face, hands and feet were a grayish, indigo blue. Particularly striking were the mucous membranes of the mouth and lips. He complained chiefly of headache and weakness. Respiratory distress was conspicuous by its absence. On attempting to leave the bed he collapsed. He was orientated, and his sensorium was clear. Hyperreflexia of the

extremities, slight ankle clonus and a positive Babinski sign on the left side were noted during the height of the cyanosis. A tentative diagnosis of methemoglobinemia due to ammonium nitrate was made. A specimen of blood taken for examination was dark reddish brown. Methemoglobin was identified spectroscopically. During this episode the carbon dioxide-combining power was 26.5 per cent by volume, the urea 73.5 mg. per hundred cubic centimeters, and creatinine, 5.2 mg.

All medication was discontinued, and the patient was placed in an oxygen tent for several hours. It is doubtful whether this last measure was of any value. In twelve hours the cyanosis had disappeared, and the patient felt much as he did before the onset of the attack. The abnormal neurologic findings had disappeared. It was interesting to compare the color of samples of venous blood as the cyanosis receded. The dark reddish-brown color of the earlier specimens, which on shaking and exposure to air failed to turn a lighter red, was replaced by color and behavior which approached the normal.

The results of subsequent chemical examinations of the blood were not significantly different from those obtained during the period of methemoglobinemia. The carbon dioxide-combining power rose to 30 per cent by volume and later to 50 per cent.

Because of the already existing severe acidosis and increasing renal insufficiency, it was not deemed advisable to try again other acid-producing salts.

Summary.—In a man 48 years old man with chronic glomerulonephritis and renal insufficiency severe methemoglobinemia suddenly developed, following the administration of 50 Gm. of ammonium nitrate in eight days.

CASE 3.—*History.*—B. S., an elderly woman, 73 years of age, was admitted to the hospital on Oct. 17, 1931, with complaints of dyspnea and precordial pain of four years' duration and swelling of the lower extremities of two years' duration.

Physical Examination.—The patient was well developed and well nourished. There were an ashen gray pallor of the face and a contrasting cyanosis of the lips. The heart was markedly enlarged to the left, and its base was broadened on percussion. A loud systolic murmur overshadowed both apical sounds. The sounds at the base were poorly heard. The blood pressure was 102 systolic and 60 diastolic. There were signs of pulmonary congestion and thickened pleura at the bases of the lungs. The edge of the liver was palpable at the level of the umbilicus. The spleen was also slightly enlarged. There was marked edema of the lower extremities up to the sacrum.

Laboratory Data.—The result of examination of the urine for albumin was 2 plus; its specific gravity was fixed between 1.012 and 1.018. Occasional hyaline casts were present. The blood urea nitrogen ranged between 20 and 32 mg. per hundred cubic centimeters. The electrocardiogram showed auricular fibrillation with a slow ventricular rate.

Diagnosis.—The diagnosis was antecedent hypertension with disease of the coronary artery, multiple myocardial infarctions, congestive heart failure and arteriosclerosis of the kidneys.

Course and Treatment.—On admission to the hospital the patient weighed 73.6 Kg. Following restriction of fluids, a salt-poor diet, the administration of 6 Gm. of ammonium nitrate daily and two injections of salyrgan, her weight dropped to 60 Kg. in nine days. Edema of the lower extremities had practically disappeared. On Oct. 26, 1931, diuretic therapy was discontinued because of a sudden chill and a rise in temperature to 102.5 F. There was no change in the cardiac condition, and the picture was attributed to an acute bronchitis. The elevation in temperature lasted about one week. At the end of this time the patient

was again placed on ammonium nitrate as a diuretic to supplement the action of salyrgan. On the evening of Dec. 13, 1931, she was noted to be diffusely cyanotic, although there were no additional symptoms. An hour later she began to complain of severe headache and of feeling uncomfortable. The dyspnea previously present was not increased. The pulse rate was 84 and the blood pressure 110 systolic and 44 diastolic. There was a striking deep blue cyanosis over the entire body, which was most marked on the lips and the visible mucous membranes. Under artificial illumination there was a greenish tinge to the cyanosis. No abnormal neurologic signs were elicited. A specimen of venous blood was dark reddish brown and did not change on shaking and exposure to the air. Methemoglobin was demonstrated spectroscopically.

All medication was discontinued. In twelve hours the patient was much improved, and in twenty-four hours all cyanosis had disappeared. The course since that time has been uneventful. During the cyanotic phase, the carbon dioxide-combining power of the blood was 31.5 per cent by volume. It rose three days later to 52 per cent.

Summary.—In a woman, 73 years old, with disease of the coronary artery, congestive heart failure and renal arteriosclerosis marked methemoglobinemia developed after the ingestion of 6 Gm. of ammonium nitrate a day for forty-two days, a total of 252 Gm..

CASE 4.—*History.*—L. B., a Jewish woman, 65 years of age, complained of dyspnea and weakness of three years' duration. In 1930 midtibial amputation of the left leg was performed because of arteriosclerotic gangrene. Diabetes mellitus was discovered at that time. On Feb. 9, 1931, she was admitted to Montefiore Hospital because of tingling and numbness in the fingers of both hands.

Physical Examination.—The patient was an emaciated woman confined to bed. The eyes showed bilateral lenticular opacities and numerous pinpoint-sized absorption spots and hemorrhages in the retinas. The right half of the chest was smaller than the left, and there were signs of a fibroid tuberculosis in both lungs, more on the right side. The heart was slightly enlarged to the left. The second aortic sound was accentuated, and the blood pressure was elevated to 180 systolic and 80 diastolic. There was marked sclerosis of all the peripheral palpable vessels. The edge of the liver was barely felt at the costal border. The fingers and toes were moderately cyanosed. The knee jerk and ankle jerk of the remaining extremity were not obtained. The biceps and triceps reflexes were very weak.

Laboratory Data.—The specific gravity of the urine was fixed between 1.013 and 1.015. Albumin 2 plus and granular and hyaline casts were nearly always present. Glycosuria was found occasionally. The blood sugar fluctuated between 300 and 500 mg. per hundred cubic centimeters and the urea nitrogen between 18.5 and 28 mg. A mild secondary anemia was present.

Diagnosis.—The diagnosis was generalized arteriosclerosis, diabetes mellitus, hypertension, arteriosclerotic heart disease, fibroid tuberculosis, compensated arteriolosclerosis of the kidneys and status after amputation of the leg.

Course and Treatment.—The patient was placed on a diabetic diet and was given 20 units of insulin daily. On Oct. 28, 1931, signs of congestive heart failure were noted. She was given 2 Gm. of ammonium nitrate three times a day, with a favorable response. On Dec. 11, 1931, she complained of headache, nausea and dizziness. The episode was transitory, and no immediate cause could be found. Three days later she again complained of headache and nausea. This time a moderate generalized cyanosis was noted in contrast to the usual pallor. The color was a darker blue than in cardiac cyanosis. No abnormal neurologic reflexes were noted. A specimen of blood taken at this time was dark chocolate brown

and did not change on shaking and exposure to the air. The ammonium nitrate was discontinued, and within twelve hours she returned to her previous status. The episode was interpreted as a mild methemoglobinemia. The total amount of ammonium nitrate taken was 6 Gm. a day for forty-six days.

Summary.—In a 65 year old woman with marked arteriosclerosis, arteriosclerotic heart disease, diabetes mellitus and impaired renal function, mild methemoglobinemia developed following the administration of 276 Gm. of ammonium nitrate in forty-six days.

COMMENT

In case 1 the diagnosis of methemoglobinemia was not suspected at the beginning. The blood was not examined spectroscopically, but its dark chocolate brown color and its failure to turn to a lighter red on shaking and exposure to the air were noted at the time. In the other patients the blood behaved similarly. The presence of methemoglobin was confirmed spectroscopically.

It is interesting to note that in the nine cases reported in the literature, including the four reported here, seven patients had renal lesions. Although gastro-intestinal dysfunction is emphasized as an important factor,[4] it was absent in my four patients. Keith and his co-workers [6] have shown that patients with renal insufficiency who have an increased nitrate content in the blood and delayed excretion in the urine have no particular tendency to develop methemoglobinemia. The reduction of nitrate to nitrite probably occurs in the gastro-intestinal tract, but how it is brought about and how it may be prevented in patients receiving ammonium nitrate are at present not understood.

In the previous reports on the toxic action of ammonium nitrate the presence of ankle clonus, hyperreflexia and a positive Babinski sign in the patients during the time they were markedly cyanosed had not been noticed. These neurologic manifestations are probably the result of a cortical irritation arising from the accompanying anoxemia.

The occurrence of transient methemoglobinemia as a toxic manifestation has not led my associates and me to discontinue the use of ammonium nitrate. It is still the best of the acid-producing drugs at our disposal. Discontinuance of the drug at the first indication of cyanosis is the only treatment necessary. When the clinical condition of the patient necessitates the administration of ammonium nitrate in large doses over a longer period, we now omit the drug on every fifth or sixth day. In very susceptible patients it might be advisable to resort to ammonium chloride rather than to the nitrate.

SUMMARY

The reported instances of transient methemoglobinemia due to ammonium nitrate are reviewed, and four additional cases are reported. An unusual feature in two of these was the evidence of cortical irritation during the height of the cyanosis.

ENDEMIC NUTRITIONAL EDEMA

II. SERUM PROTEINS AND NITROGEN BALANCE

JOHN B. YOUMANS, M.D.
AUSTIN BELL, M.D.
DOROTHY DONLEY, M.D.
AND
HELEN FRANK, A.B.
NASHVILLE, TENN.

In the preceding paper [1] the clinical findings in thirty-one patients with edema, believed to be nutritional in nature, are reported. In addition to an initial determination of the serum proteins in thirty-one patients with edema, repeated determinations were made in eleven cases over periods of from a few weeks to more than a year, under varying conditions of diet and treatment. Studies of nitrogen balance were made in two cases. The results of these studies are reported in this paper.

METHODS

With two exceptions, the subjects were studied and followed exclusively in the outpatient department.

Serum Proteins.—The initial determinations of serum protein were made in some instances at the time the patient was first seen; more often they were made a few days later, and frequently at a time when the edema was lessening. The blood was obtained after an overnight fast or several hours after a light breakfast. It was drawn without stasis or exposure to the air, transferred to a clean centrifuge tube under oil, allowed to clot and the clot allowed to retract. The serum was pipetted off after centrifuging. In the first few cases the total serum proteins alone were determined by the refractometer. In most of the cases the albumin and globulin fractions were separated by the method of Howe,[2] using 22.5 per cent sodium sulphate. This procedure was carried out in a constant temperature box in which all the apparatus and reagents were kept at 37 C. After precipitation the samples were allowed to stand over night. Cloudy filtrates were refiltered until clear or were discarded. In a few of the earlier cases the total protein, albumin and globulin were determined by the colorimetric method of Greenberg.[3] In the

From the Department of Medicine, School of Medicine, Vanderbilt University.

1. Youmans, John B.; Bell, A., Donley, D., and Frank, H.: Endemic Nutritional Edema: I. Clinical Findings and Dietary Studies, Arch. Int. Med. **50**:843 (Dec.) 1932.

2. Howe, P. E.: The Use of Sodium Sulphate as the Globulin Precipitant in the Determination of Proteins in the Blood, J. Biol. Chem. **49**:93, 1921.

3. Greenberg, D. M.: The Colorimetric Determination of the Serum Proteins, J. Biol. Chem. **82**:545, 1929.

majority the total nitrogen of the serum and the albumin nitrogen of the filtrate were determined by the macro-Kjeldahl method. Distillation was carried out without transfer to a separate flask, distilling into fiftieth-normal acid and titrating with fiftieth-normal sodium hydroxide, using alizarin as the indicator. All determinations were made in duplicate and checks were made on the reagents. The total protein nitrogen was calculated by subtracting the nonprotein nitrogen, determined separately, from the total nitrogen. Albumin nitrogen was represented by the difference between the nitrogen of the filtrate and the nonprotein nitrogen. The factor 6.25 was used to convert the figures for nitrogen to protein. Globulin was calculated by the difference between the total protein and albumin.

Studies of nitrogen balance were made in two of the cases (cases 16 and 17) as follows: On admission the patient was placed on a diet corresponding as closely as possible in amounts and kind of food to that which had been eaten at home and which had previously been recorded.[1] The composition of these diets is given in the presentation of the results. Each day's diet was prepared in duplicate in the diet kitchen and weighed. One was given to the patient. The other was sent to the laboratory where the total food for the day was weighed, ground up together and dumped into a large volume of sulphuric acid. Nitrogen was determined on aliquot samples by the usual Kjeldahl method. The food not eaten by the patient was carefully saved, weighed and sent to the laboratory, where its nitrogen content was determined in a similar manner. The urine and stools were passed directly into weighed containers, carefully collected daily and sent to the laboratory. The stools were weighed, wet ashed as already described, and the nitrogen determined on aliquot samples. The complete collection of the urine was controlled by determining the creatinine content of the twenty-four hour specimen. Nitrogen determinations were made in the usual manner. Following a preliminary period on this regimen the experimental periods were begun. To separate the feces belonging to each period the stools were marked by administering a capsule of carmine lake (0.6 Gm.) at 1 p. m. on the last day of each period, and the appearance of the carmine marked the end of that period. When determinations for a single day were made, no attempt was made to separate the stools with carmine, and all stools within a twenty-four hour period were included in the previous day's determinations. After a three to four day period on the diet with a low protein content, a diet of high protein content was given. In case 17 the low protein period was followed by a three day period of low protein diet plus brewers' yeast (15 Gm. daily). This period was in turn followed by a two day period of low protein diet without yeast before the diet with a high protein content was begun. The patients were weighed daily before breakfast and the amount of edema estimated frequently, usually during the afternoon. Determinations of the serum protein were made at suitable intervals. Unfortunately it was necessary to confine the patients to bed during the greater part of the time, in order to insure accuracy in the intake of food and collection of specimens. During the latter part of the study they were allowed to spend some time in a bedside chair.

EXPERIMENTAL RESULTS

There are considerable differences in the normal standards for serum proteins adopted by various writers, particularly with respect to the normal range. These differences are due mainly to the variety of methods used, and some writers have failed to describe their methods in detail. The standards which we have adopted are essentially those of Bruck-

man, D'Esopo and Peters,[4] whose values are almost identical with those we have obtained in fifteen normal subjects (members of the staff and students). The standards are as follows: average values, total protein 7.30 per cent and albumin 5.00 per cent; globulin 2.3 per cent; normal range, total protein from 6.5 to 8.5 per cent, albumin from 4.2 to 5.7 per cent and globulin from 1.3 to 3.0 per cent. For the purpose of comparison with the present series the serum proteins of twenty-one patients without edema, who are representative of the group from which our patients with edema are drawn, are shown in table 1.

The results of the initial determinations of serum protein in the thirty-one cases are given in table 2. As has been stated, these determi-

TABLE 1.—*The Serum Protein and Calculated Colloid Osmotic Pressure; Control Determinations in Twenty-One Patients Without Edema*

Name	Serum Protein				Calculated Colloid Osmotic Pressure	Diagnosis
	Total Protein	Albumin	Globulin	Albumin/Globulin Ratio		
L. T.	7.40	4.97	2.43	2.04	42.21	Syphilis; obesity
M. T.	7.26	4.87	2.39	2.04	41.38	Pellagra (?)
M. H.	7.92	6.15	1.77	3.47	49.82	Syphilis; obesity
C. H.	6.95	4.72	2.30	2.05	40.07	Hernia
L. H.	7.02	4.88	2.14	2.28	40.97	?
W. H.	6.79	4.91	1.88	2.61	40.69	Pellagra
N. S.	7.28	4.95	2.33	2.12	41.87	Recurrent pellagra
B. A.	7.09	4.30	2.79	1.54	37.86	Obesity
M. T.	7.47	5.35	2.12	2.52	44.47	Malnutrition
A. B.	7.75	5.48	2.27	2.41	45.75	Psychoneurosis
T. J.	7.83	4.73	3.10	1.52	41.71	Syphilis
T. W.	7.65	5.23	2.42	2.16	44.15	Hemorrhoids
P. F.	6.73	4.62	2.11	2.19	38.95	Toxic neuritis, diphtheritic (old)
I. O.	7.69	5.14	2.55	2.01	43.73	Nursing mother
J. W.	7.30	5.05	2.25	2.24	42.46	Pellagra
P. H.	7.87	4.44	3.43	1.29	40.17	Pellagra
M. L.	7.64	5.43	2.21	2.45	45.25	Albuminuria (slight)
L. T.	7.50	5.16	2.34	2.20	43.47	Pellagra
C. H.	7.62	4.92	2.70	1.96	41.97	Hypertrophy of prostate
J. J.	7.66	4.46	3.20	1.39	39.87	Constitutional inferiority
M. H.	7.29	5.02	2.09	2.40	41.93	Undernutrition (?)
Average	7.41	4.98	2.41	2.13	42.25	

nations were often made some days after the patients were first seen and frequently at a time when the edema was subsiding. In the first three cases the total protein alone was determined, but they have been included in the series because they were among the first in which the condition was recognized and were typical examples of the disease, which was subsequently studied in greater detail.

The total proteins varied but little from the normal, in most of the cases. Though below the average normal[5] in twenty-two of the cases,

4. Bruckman, F. S.; D'Esopo, L. M., and Peters, J. P.: The Plasma Protein in Relation to Blood Hydration: IV. Malnutrition and the Serum Proteins, J. Clin. Investigation **8**:577, 1930. Although the principal title of this paper refers to plasma proteins it should be noted that the subtitle refers to serum protein and that serum was used in the determinations.

5. Comparison with the average normal is of relatively little importance; comparison with the normal range is much more significant.

values below the lower range of normal were found in but five and amounts less than 6.0 per cent in only three. The albumin fraction showed more significant changes. The individual values ranged from 1.72 to 4.97 per cent, with an average of 3.95 per cent, which is below the lower limit of normal. More significantly, the individual determinations were at or below the lower limit of normal in sixteen (59 per

TABLE 2.—*Initial Serum Protein Determinations in Thirty-One Patients with Edema* *

Case	Date	Edema†	Serum Protein				Calculated Colloid Osmotic Pressure	Comment
			Total Protein	Albumin	Globulin	Albumin/Globulin Ratio		
	1929							
1	June 18	+	8.00					
2	July 19	+	7.50					
3	July 10	+	7.20					
4	July 23	+	7.00					
	1930							
5	April 5	+	7.30	2.95	4.35	0.67	30.72	
6	April 22	+	6.20	3.05	3.15	0.96	29.13	
7	May 14	+	6.70	3.90	2.80	1.40	34.87	
8	July 16	+	7.30	3.90	3.40	1.14	36.03	
9	July 23	+	7.50	3.00	4.50	0.66	31.39	
10	July 25	+	6.51	3.71	2.80	1.32	33.44	
11	July 31	+	6.50	3.90	2.60	1.50	34.47	
12	Oct. 2	+	7.87	4.81	3.06	1.57	42.23	Edema disappearing
13	Nov. 19	0	6.97	4.52	2.45	1.84	38.85	
14	Dec. 15	?‡	6.46	4.28	2.18	1.96	36.55	
	1931							
15	March 4	+	6.61	4.09	2.52	1.59	35.74	
16	March 9	+	7.91	4.31	3.60	1.28	39.51	Observed later with edema and lowered albumin
17	March 18	+	5.35	3.62	1.73	2.09	30.67	
18	March 25	+	6.50	3.94	2.56	1.53	33.10	
19	April 13	+	5.96	1.72	4.24	0.40	21.24	
20	April 23	+	5.94	3.19	2.75	1.16	29.40	
21	April 29	+	6.96	3.83	3.15	1.21	35.02	
22	April 29	+	6.83	3.89	2.94	1.32	35.07	
23	May 29	0	7.12	4.68	2.44	1.91	40.04	Edema previously
24	June 9	0	7.07	4.90	2.16	2.26	41.15	Edema previously
25	June 29	0	7.44	4.57	2.87	1.62	40.05	Edema previously
26	June 23	?	7.53	4.94	2.59	1.90	42.25	Edema off and on for 3 years; disappearing
27	July 7	+	7.23	3.87	3.36	1.15	35.73	
28	July 8	+	7.65	4.97	2.68	1.85	42.70	No edema 1 week later
29	July 23	+	6.75	4.47	2.28	1.93	38.14	Edema disappearing
30	July 29	+	6.69	4.50	2.19	2.05	38.20	Edema disappearing
31	July 29	+	6.93	4.14	2.79	1.48	36.64	Edema of face only

* The clinical data on these subjects are given in the preceding paper.[1]

† No attempt was made to record the amount of edema at the time these determinations were made.

‡ In the statistical treatment of these data the cases marked ? have been considered to be without edema.

cent) of the cases. In sharp contrast to the albumin, the globulin was above normal average in all but five cases, and in nine cases was above the upper limit of normal. Values below the normal lower limit were not found in a single case. The albumin-globulin ratio, while less significant than the actual amounts of the two fractions, is of some interest in view of the strong tendency toward an increase in globulin in this series. Low ratios were frequent, the average being well below the average normal, while individual ratios below the lower normal were

TABLE 3.—*Repeated Determinations of Serum Proteins in Patients with Edema*

Case	Date	Edema*	Serum Protein: Total Protein	Albumin	Globulin	Albumin/Globulin Ratio	Calculated Colloid Osmotic Pressure	Comment
3	1929 July 7	+	7.2					7/10: high protein diet with disappearance of edema in one month; hemoglobin increased
	1931 July 3	+	7.07	4.56	2.71	1.61	38.15	Return of edema; loss of weight
	Aug. 10	±	6.99	4.35	2.64	1.65	37.95	Edema in evenings
	Aug. 17	±	6.91	4.27	2.64	1.62	37.35	Diet unsatisfactory
5	1930 April 5	+	7.30	2.95	4.35	0.68	30.72	
	May 30	±	7.48	3.60	3.88	0.93	34.71	Brewers' yeast 15 Gm. daily
	June 9	±	9.60	4.60	5.00	0.92	44.43	High protein diet
	June 19	+	9.60	3.50	6.10	0.57	38.29	High protein diet again advised
	July 7	0	8.50	2.80	5.70	0.49	32.23	
	July 21	0	7.70	4.10	3.60	1.14	37.93	
	Aug. 25	0	7.30	5.00	2.30	2.17	42.19	
	Oct. 13	0	7.85	4.68	3.17	1.48	41.47	
	Dec. 8	0	8.30	4.82	3.48	1.39	43.33	
6	April 22	++	6.20	3.05	3.15	0.97	29.13	Increased protein (milk) ordered
	May 13	+	8.20	2.95	5.25	0.56	32.48	
	May 28	+	6.70	3.79	2.91	1.30	34.25	
7	May 14	+	6.70	3.90	2.80	1.39	34.41	Bitter tonic
	May 21	+	8.15	2.65	5.50	0.48	30.71	Brewers' yeast, 15 Gm. daily
	June 10	0	7.70	4.10	3.60	1.13	37.93	High protein diet advised
	Oct. 13	0	7.21	4.62	2.59	1.78	39.88	
	Nov. 12	?	6.62	4.39	2.23	1.97	37.45	
	1931 March 20	+	6.61	4.39	2.22	1.98	37.43	
	Aug. 12	+	7.11	4.68	2.43	1.92	40.03	No edema 4 weeks later
9	1930 July 23	+++	7.50	3.00	4.50	0.67	31.40	Brewers' yeast (15 Gm. daily) for 1 week; then high protein diet added
	Aug. 19	++	6.50	3.80	2.70	1.41	33.92	
	Oct. 1	?	8.01	5.25	2.76	1.90	44.97	
13	Nov. 19	?	6.97	4.52	2.45	1.84	38.86	Edema present before and after this examination; absent in May, 1931
	1931 July 6	+	7.09	4.10	2.99	1.37	36.74	Edema returned
	July 13	+	7.46	4.61	2.85	1.62	40.32	Marked diuresis and loss of edema 2 days before
	July 20	+	6.99	4.34	2.65	1.64	37.89	Diet probably unsatisfactory
	Aug. 17	+	7.34	4.46	2.88	1.55	39.25	
18	March 20	+	7.80	3.70	4.10	0.77	35.89	
	March 25	+	6.50	3.94	2.56	1.54	34.70	
	April 6	0	6.58	4.06	2.52	1.61	35.52	Diuresis day before; bitter tonic
	April 13	0	6.00	3.97	2.03	1.96	32.06	
19	April 13	++++	5.96	1.72	4.24	0.40	21.97	Gain of 2 Kg. since admission on 4/6/31 in spite of digitalization
	April 27	++	6.68	3.58	3.10	1.14	32.67	Brewers' yeast, 15 Gm. daily, since 4/21/31; loss of 2.8 Kg.
	May 11	+	6.33	3.37	2.76	1.29	32.30	Gain of 1.3 Kg.; high protein diet
	May 18	±	6.74	3.64	3.10	1.17	33.50	Loss of 1.3 Kg.
	May 25	±	7.07	3.87	3.20	1.21	35.42	
	July 6	0	6.83	3.91	2.92	1.34	35.17	Weight constant
	July 27	0	8.94	4.49	4.45	1.01	42.53	Loss of 1.6 Kg.
	Aug. 17	+	6.94	3.71	3.23	1.15	34.27	Diet probably unsatisfactory
	Aug. 31	±	7.04	3.81	3.23	1.18	35.03	Gained 1.8 Kg.
	Sept. 14	±	6.98	3.82	3.16	1.21	34.96	Slight loss of weight
21	April 29	+	6.98	3.83	3.15	1.22	35.02	Gain of 7.3 Kg. in past eight weeks
	May 20	+	7.18	4.03	3.15	1.28	36.53	High protein diet begun 5/13/31

* In the statistical use of these data the edema was considered absent in the cases marked ? and present in those marked ±.

found in thirteen. In only one case was the ratio as high as the average normal.

The presence or absence of edema is recorded with the serum protein values in table 2, but for the purpose of presenting the relation of the edema to the serum proteins the results of the initial determinations have been grouped with the results of repeated determinations made in eleven of the cases (tables 3, 4 and 5). The inclusion of cases without edema in table 2 is due to the fact that some patients who had edema when first seen were free from edema when the serum protein was determined. Thus in four cases (cases 13, 23, 24 and 25) edema was

TABLE 4.—*Nitrogen Metabolism, Serum Protein, Body Weight and Edema in Case 16*

	Nitrogen*				Serum Protein			Nonprotein			
		Output									
Date, 1931	Intake, Gm.	Total, Gm.	Urine, Gm.	Feces, Gm.	Total, per Cent	Albumin, per Cent	Globulin, per Cent	Nitrogen, Mg. per 100 Cc.	Wt., Kg.	Edema	Comment
March 9†	.....	.....	.....	....	7.91	4.31	3.60	27	81.6	++++	
March 16	.....	.....	.....	....	....	....	....	..	78.8	++	Admission to hospital; low protein diet‡
March 17	7.29	8.98	7.24	1.74	7.72	4.35	3.37	27	77.2	+	
March 18	6.31	8.62	7.65	0.97	....	....	....	..	77.0	±	
March 19	6.57	8.38	7.31	1.07	....	....	....	..	76.6	+	
March 20	6.50	8.31	7.31	1.00	....	....	....	..	77.0	++	
March 21	12.41	10.40	9.15	1.25	7.43	4.16	3.27	38	76.8	++	High protein diet begun
March 22	13.22	10.53	9.50	1.03	....	....	....	..	77.6	+	
March 23	13.78	13.82	12.40#	1.42	....	....	....	..	77.0	+	
March 24	14.14	11.72	10.87	0.85	7.30	3.91	3.39	34	76.5	+	
March 25	14.61	11.26	9.28	1.98	....	....	....	..	76.5	±	
March 26	.....	.....	.....	....	7.48	4.16	3.32	24	76.8	±	Discharged from hospital
March 30†	.....	.....	.....	....	7.36	4.18	3.18	24	78.3	±	
April 6†	.....	.....	.....	....	7.12	4.02	3.10	25	77.8	±	

* Actual daily determinations.
† Observed in outpatient department.
‡ All diets in the hospital were planned to contain a minimum protective amount of vitamins. Water was allowed ad libitum, and the sodium chloride intake was kept constant at about 5 Gm.
# This inconsistent value is unexplained and may be an error.

absent at the time of the initial determination of serum protein and the albumin was within normal limits. Case 13 on subsequent observation showed edema and a low serum albumin. In five cases (cases 12, 16, 28, 29 and 30) edema was present when the albumin was at or above the lower limit of normal. In cases 12, 28, 29 and 30, the edema had disappeared within a week after the determinations were made, and was probably disappearing at the time of the examination. Case 16 subsequently showed edema and serum albumin below normal. In case 27, edema was questionably present with an albumin content of 4.94 per cent. In this case the edema, which had been present intermittently for years, was present before the determination of serum protein was made, but was absent later and was probably disappearing when the blood was studied.

Repeated determinations of the serum protein over periods of from three weeks to more than two years were made in eleven of the cases. The serum protein values under varying conditions of diet and treatment and their relation to the presence or absence of edema are pre-

TABLE 5.—*Nitrogen Metabolism, Serum Protein, Body Weight and Edema in Case 17*

	Nitrogen*				Serum Protein			Nonprotein Nitrogen,			
		Output									
Date, 1931	Intake, Gm.	Total, Gm.	Urine, Gm.	Feces, Gm.	Total, per Cent	Albumin, per Cent	Globulin, per Cent	Mg. per 100 Cc.	Wt., Kg.	Edema	Comment
March 18†	.....	.....	.....	....	5.35	3.62	1.73	35	56.7	++++	
March 26	.....	.....	.....	....	....	....	....	..	50.9	++++	Admitted to hospital; low protein diet‡
March 28	5.66	5.96	4.77	1.09	6.52	3.77	2.75	30	49.3	++++	
March 29	5.66	5.96	4.77	1.09	....	....	....	..	48.6	++++	
March 30	5.66	5.96	4.77	1.09	6.40	3.83	2.57	30	47.5	+++	
March 31	5.66	5.96	4.77	1.09	....	....	....	..	47.0	++	
April 1	.....	.....	.....	....	....	....	....	..	47.6	++	Low protein diet continued
April 2	.....	.....	.....	....	....	....	....	34	47.0	++	
April 3	5.66	7.02	6.28	0.74	....	....	....	..	46.9	++	Brewers' yeast, 15 Gm. daily
April 4	5.66	7.02	6.28	0.74	7.07	4.35	2.72	30	46.6	+	
April 5	5.66	7.02	6.28	0.74	....	....	....	..	46.7		
April 6	.....	.....	.....	....	....	....	....	..	46.4	+	Low protein diet without yeast
April 7	.....	.....	.....	....	....	....	....	..	46.4	±	
April 8	14.24	10.70	9.38	1.32	....	....	....	30	46.0	±	High protein diet begun
April 9	14.24	10.70	9.38	1.32	....	....	....	..	46.3		
April 10	14.24	10.70	9.38	1.32	....	....	....	..	46.4	±	
April 11	12.13	11.49	10.29	1.29	7.47	4.75	2.72	33	46.3		
April 12	12.13	11.49	10.29	1.29	....	....	....	..	46.2	±	
April 13	12.77	11.67	10.12	1.55	....	....	....	..	46.4	+	
April 14	12.77	11.67	10.12	1.55	7.36	4.53	2.83	33	46.8	++	
April 15	12.22	11.15	9.74	1.42	....	....	....	..	46.7	+	
April 16	12.22	11.15	9.74	1.42	....	....	....	..	46.6	±	
April 18	.....	.....	.....	....	7.44	4.57	2.87	32	46.0	±	Discharged from hospital
April 27	.....	.....	.....	....	7.43	4.68	2.75	30	48.4	0	
August 5	.....	.....	.....	....	7.53	5.07	2.46	20.6	....	0	

* Average daily intake and output for the periods inclosed in brackets. In the first and last periods daily determinations were made.

† Observed in the outpatient department.

‡ All diets in the hospital were planned to contain a minimum protective amount of vitamins. Water was allowed ad libitum, and the sodium chloride intake was kept constant at about 5 Gm.

sented in tables 3, 4 and 5. In order to show the relation between the serum protein levels and the edema, the initial values in all of the cases have been grouped with those obtained on repeated examination, giving a total of eighty-three determinations of total proteins and seventy-nine determinations of the serum albumin and globulin.

The total serum proteins were determined eighty-three times in thirty-one patients. They were at or below the lower limit of normal in twelve examinations, with edema present at the time in ten. In sixty-seven instances the total protein was within the normal limits, with edema present in fifty. In four instances the total protein was higher than normal, with edema present in two. However, of the fifty instances in which edema was present with a normal or increased total protein, this level of total protein was the result of a globulin above the average normal in forty-seven, and above the upper limit of normal in twenty-six. In each of the four instances in which the total protein was abnormally high, the globulin was higher than normal.

Among the seventy-nine determinations of albumin, values at or below the lower normal were found in forty-five, with edema present at the time in thirty-nine and absent in six. The albumin was within the normal range in thirty-four instances, in nineteen of which edema was present. However, of the nineteen instances in which edema was present with a normal serum albumin, the latter was very near the lower limits of normal in ten. It should be emphasized that no attempt has been made to correlate the degree or the stage of edema (i.e., whether developing or disappearing) with the level of serum proteins.

The findings with respect to the globulin are in some respects the opposite of those in the case of albumin. In no instance was the globulin value found to be below the normal limits. Values within the normal range were found in forty-six analyses, with edema associated in thirty-one instances. The globulin was above the upper normal limit in thirty-three instances with an associated edema in twenty-seven.

The colloid osmotic pressure in these cases is of interest in view of the lack of correlation between the presence of edema and the amounts of total protein. They have been calculated by means of Govaerts'[6] factors (tables 2 and 3).[7] In thirty-nine instances the values were below those which Govaerts, using direct measurement, found in normal persons. Edema was associated with the lowered osmotic pressure in thirty-four. Normal values were found in forty, with edema present in twenty-five.

The relation between edema and the serum proteins is graphically represented in chart 1. It is seen that there is no correlation between the edema and the total proteins. There is some apparent relation in the case of albumin, although, owing to causes which will be discussed

6. Govaerts, P.: Influence de la teneur du sérum en albumines et en globulines sur la pression osmotique des protéines et sur la formation des oedemes, Bull. Acad. roy. de méd. de Belgique **7**:356, 1927.

7. The colloid osmotic pressures calculated from the data in tables 4 and 5 are included.

later, it is not very close. In the case of globulin there is a tendency toward a relation the opposite of that with albumin, in that high values of globulin are often found associated with edema. A similar finding was noted by Bruckman, D'Esopo and Peters.[4] Correlation is better in the case of total colloid osmotic pressure than with total protein.

In the cases in which repeated observations were made, it will be observed that there was a tendency for the edema to lessen as the albumin rose and to disappear as the albumin reached normal levels. In a number of instances, however, edema persisted for some time after the albumin had reached normal. The reverse was also true, and in those cases in which the albumin gradually declined, edema occasionally

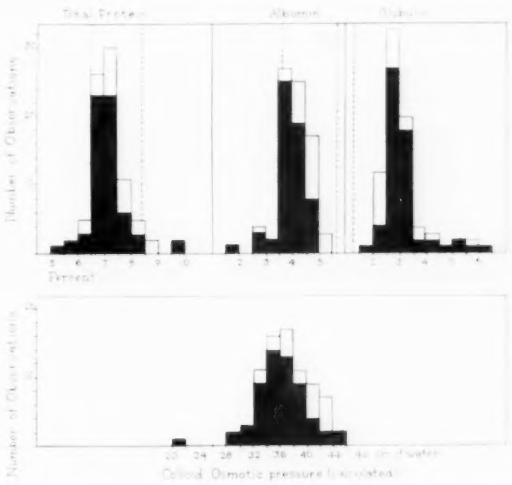


Chart 1.—The relation of the serum proteins and of the calculated colloid osmotic pressures of the serum to the edema. The black areas indicate the presence of edema; the broken lines, the "normal" range.

failed to appear until some time after the albumin had sunk to a level below normal. In most of the cases the determinations were made too infrequently to determine accurately the time necessary for the albumin to return to normal. Usually there was some increase fairly soon after the diet was increased, but it was several weeks before the proteins reached their maximum (optimum?) levels. While this may have been partly due to a failure to take the diet recommended, the results in the cases of the two patients studied in the hospital and in Ling's [8] cases

8. Ling, S. M.: Change of Serum Proteins in Undernutrition, Chinese J. Physiol. **5**:1, 1931.

suggest that a considerable time is necessary before the proteins reach their normal level in these cases.

The globulin fluctuated rather widely from normal to abnormally high levels, but showed a tendency toward two distinct types of change. The first was a rise at the onset of improvement after treatment, which seemed to herald a rise in albumin. The second was a fall as the albumin increased.

The two patients who were admitted to the hospital for studies of nitrogen metabolism lost a great deal of weight and edema as soon as they were admitted and before they were placed on the diet with a high protein content. In one of them (case 17) there was a loss of 5.8 Kg. between the time she was first seen in the outpatient department and the time that she returned for admission to the hospital. This loss of edema is not apparent in the tables because of the system of grading the edema which was used. In both cases the initial edema was much greater than the symbols indicate. The significance of this loss of edema is discussed later, but it may be pointed out that it is responsible for the lack of greater changes during the treatment in the hospital.

Both patients showed a slight negative nitrogen balance on the low protein diet which they were taking on admission and which was continued during the first few days in the hospital. In case 16, the patient was first placed on a diet containing approximately 41 Gm. of protein, 137 Gm. of carbohydrate, 76 Gm. of fat and 1,396 calories. During a four days period on this diet the nitrogen intake was 26.67 Gm. and the output 34.29 Gm. During the second period of five days she was given a diet of 92 Gm. of protein, 169 Gm. of carbohydrate, 77 Gm. of fat and 1,800 calories. During this period she took in 68.16 Gm. of nitrogen of which she retained 10.43 Gm. Actually the protein intake was somewhat less during the first two days and the retention was somewhat greater at the end than at the beginning of the period. Unfortunately it was impossible to keep her in the hospital longer. Except for the large initial loss of weight referred to, there was little change during this period. Four days after discharge she had gained 1.5 Kg. and was practically free from edema. Five days later the weight had decreased slightly, but there is reason to believe that the diet was unsatisfactory. The serum albumin showed a slight drop during the period of the diet low in protein, and thereafter remained practically constant.

The second patient (case 17) was given, on admission, a diet of 35 Gm. of protein, 153 Gm. of carbohydrate, 46 Gm. of fat and 1,166 calories, a somewhat larger amount of calories than she had been receiving prior to admission, and near her basal requirement. During the first period the nitrogen intake was 22.66 Gm. and the output 23.85 Gm. During the second period the same diet was continued but brewers' yeast

(15 Gm. daily) was added. The nitrogen intake during this three days period was 17 Gm. and the output 21.07 Gm. After an interval of two days on the low protein diet without yeast she was given a diet consisting of 74 Gm. of protein, 88 Gm. of fat, 176 Gm. of carbohydrate and 1,792 calories. The nitrogen intake during this nine days period was 116.96 Gm., of which she retained 16.22 Gm. However, the actual nitrogen intake was greater during the first part of the period, averaging nearly 90 Gm. for the first three days. The edema, which was only slight after the initial loss of weight, gradually lessened and was practically absent on discharge. It should be remembered that the changes in weight in these experiments are the result of two opposite changes, the loss of edema and the improved nutrition, and that in a short period the changes in weight need not parallel the changes in edema. When seen in the outpatient department three days after discharge, the patient was without edema and had gained 2.7 Kg. The serum albumin rose slightly even before she was placed on the diet of high protein content, and was accompanied by a decrease in the edema. During the latter part of the period in the hospital the albumin was slightly below the amount found on April 11, and during this period the weight was stationary. The maximum amount of albumin was attained some time after discharge.

COMMENT

In general, the results of this study show that the edema in these cases was associated with a normal total protein, a normal or increased globulin and a slight to moderate reduction in the serum albumin. The last finding is the most important; the reduction, while not great, is believed to be significant, and the fact that the deviation from normal was small is consistent with the generally mild nature of the disease. Greater reductions in the serum albumin have been reported by other writers. Several factors are probably responsible for this difference between their results and ours. In some instances variations in methods and standards may be partly responsible. Much more important is the difference in the severity of the disease, the circumstances under which our studies were made, and their influence on the relation between the occurrence of edema and the level of the serum proteins. Lowered osmotic pressure caused by a reduction of serum protein is only one of the two principal factors thought at present to be concerned in the formation of this type of edema, and determines only a "tendency toward edema." If one accepts the hypothesis of Starling,[9] the occurrence or nonoccurrence of the edema depends primarily on the balance between colloid osmotic pressure and intracapillary pressure; edema is

9. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, J. Physiol. **19**:312, 1895-1896.

the result of a disturbance in this balance. Other factors, such as "tissue pressure" and electrolyte and hydrogen iron concentration, are probably of secondary importance only, the latter through their influence on the Donnan equilibrium. An increase in capillary pressure can cause a filtration of water from the blood into the tissue spaces in the presence of normal amounts of protein.[10] Krogh, Landis and Turner [11] have recently shown that the erect human being is always near edema. Therefore, even a slight reduction in the serum protein below the lower limits of normal might result in the formation of edema, provided the other factors remain constant (normal).

All the patients studied were ambulatory patients more or less engaged in their usual activities. It is to be expected, therefore, that edema would occur at higher concentrations of serum proteins than in patients who were studied in the hospital and whose activity was greatly restricted. Burger [12] has emphasized the influence of exercise in increasing the formation of edema in these cases. Furthermore, the amount of edema may be expected to parallel more or less closely the decrease in serum protein, and therefore the edema in most of these cases should be much less than in those patients whose serum proteins are greatly reduced, as was actually the case. On the other hand, because of the effect of recent muscular exercise [13] and standing position,[14] higher values for serum proteins may have been present temporarily at the time the blood was drawn.

The influence of physical activity is reflected in the absence of a sharp, critical level of serum albumin, such as has been described by Weech and Ling in "famine edema" [15] and by Moore and Van Slyke [16]

10. Drury, A. N., and Jones, N. W.: Observations upon the Rate at Which Edema Forms When the Veins of the Human Limb Are Congested, Heart **14**:55, 1927.

11. Krogh, A.; Landis, E. M., and Turner, A. H.: The Movement of Fluid Through the Human Capillary Wall in Relation to the Venous Pressure and to the Colloid Osmotic Pressure of the Blood, J. Clin. Investigation **11**:63, 1932.

12. Burger, M.: Die Ödemkrankheit, Ergebn. d. inn. Med. u. Kinderh. **18**:189, 1920.

13. Rowe, A. H.: The Effect of Muscular Work, Diet and Hemolysis on the Serum Proteins, Arch. Int. Med. **19**:499 (April) 1917.

14. Thompson, W. O.; Thompson, P. K., and Dailey, M. E.: The Effect of Posture upon the Composition and Volume of the Blood in Man, J. Clin. Investigation **5**:573, 1928. Ni, T., and Rehberg, P. B.: On the Influence of Posture on Kidney Function, J. Physiol. **71**:331, 1931.

15. Weech, A. A., and Ling, S. M.: Nutritional Edema: Observations on the Relation of the Serum Proteins to the Occurrence of Edema and to the Effect of Certain Inorganic Salts, J. Clin. Investigation **10**:869, 1931.

16. Moore, N. S., and Van Slyke, D. D.: The Relationship Between Plasma Specific Gravity, Plasma Protein Content and Edema in Nephritis, J. Clin. Investigation **8**:337, 1930.

and by Peters and his associates[17] in cases of chronic renal edema. Because of the inability to measure and control the factors, other than the amounts of protein, concerned in the production of edema, a sharp critical level of the latter is not apparent in our cases. The failure to show a critical level of serum albumin is also partly due to the variations in serum globulin and to the "lag" in the formation or disappearance of edema with changes in the concentration of protein. As is shown in the tables, when a normal or nearly normal value for albumin was found in association with edema, it almost always occurred at a time when the edema was receding but had not entirely disappeared. In many cases the edema was absent a short time later. This lag in the edema will explain many of the discrepancies in the relation between the edema and the albumin concentrations. Although studies were not made in the case of ambulatory patients, there is no reason to believe that intracapillary pressure in these patients was higher than in normal persons under similar conditions. The venous pressure was determined by direct measurement in the two patients who were admitted to the hospital (cases 16 and 17). In both instances normal values, 10 and 6 cm. of water respectively, were found. These pressures are, of course, lower than those that existed during periods of normal activity.

The total colloid osmotic pressure of the serum is of interest in view of the occurrence of edema with normal total proteins and only slight to moderate reductions in serum albumin. The calculated values in our patients are in general slightly below the calculated normal average and also slightly below the values that Govaerts[6] found by direct measurement in normal persons. As would be expected, for the reasons already discussed, they are considerably higher than those which have been reported in other types of edema.[18] Fahr, Kerhof and Conklin[19] have recently reported colloid osmotic pressures in normal subjects, determined by direct measurement, considerably below those found by Govaerts. This is of little significance in the present discussion, however, since our figures were obtained by calculation using Govaerts'

17. Peters, J. P.; Bruckman, F. S.; Eisenman, A. J.; Held, P. N., and Wakeman, A. M.: The Plasma Proteins in Relation to Blood Hydration: VI. Serum Proteins in Nephritic Edema, J. Clin. Investigation **10**:941, 1931.

18. Govaerts.[6] Schade, H., and Claussen, F.: Die onkotische Druck des Blutplasmas und die Entstehung der renalbedingten Ödeme, Ztschr. f. klin. Med. **100**: 363, 1924. Mayrs, E. B.: The Functional Pathology of Nephritis, Quart. J. Med. **19**:273 (April) 1926. Fahr, Z.; Kerhof, A., and Conklin, Claire: Osmotic Pressure of Plasma Proteins in Nephritis, Proc. Soc. Exper. Biol. & Med. **28**:720, 1931.

19. Fahr, Z.; Kerhof, A., and Conklin, Claire: Normal Osmotic Pressure of the Plasma Proteins in Man, Proc. Soc. Exper. Biol. & Med. **28**:718, 1931.

factors and would be correspondingly lowered if the latter were shown to be too high.

Certain secondary factors, particularly the intermittent and chronic nature of the disease and the intake of water and salt, may have influenced the development of edema in our cases. Edema develops more easily following an initial attack, possibly because of a lessened "tissue pressure" owing to a loss of tissue elasticity. Many of the patients had had previous attacks and several had been edematous at intervals for years. Variations in salt and water intake are known to have a considerable influence on this type of edema. Peters and his collaborators [17] have shown that in nephritic edema associated with lowered proteins, variations in salt and water intake have a marked influence on the edema unless the proteins are at a very low level. With an exception in the case of the two patients who were the subjects of the studies of nitrogen balance in which the salt intake was controlled, no attempt was made to control the salt and water intake in our cases.

The possibility that an injury to the capillary endothelium occurred as a result of continued dietary insufficiency has been considered. Edema due to this cause should be characterized by an edema fluid with a protein content similar to that of the blood plasma. Unfortunately the edema was too slight in most of the cases to permit obtaining samples of edema fluid free from contamination with blood. In one patient (case 17) a small amount of edema fluid was obtained which showed a high concentration of protein, but slight contamination with blood rendered the result unreliable. Edema fluid obtained from a case of sporadic nutritional edema, not included in this series, contained 0.6 per cent protein, of which 0.4 per cent was albumin.

An increase in the serum globulin occurred too often and was too great to be considered only coincidental. Neither is there any evidence that the high globulin content was the result of infection. It is possible that the high values are partly due to the preponderance of women in our series since the findings of Bruckman, D'Esopo and Peters [4] suggest that women have a somewhat higher globulin than men. A similar increase in globulin, however, was found by Ling [5] and Weech and Ling,[13] who ascribe to it a minor rôle in restricting the formation of edema in their cases. These authors noted, in particular, a tendency for the globulin value to rise shortly after the institution of a curative diet and before an increase in albumin occurred. A similar change was found in our cases together with a tendency for the globulin content to fall as the albumin rose. Leiter,[20] Barker and

20. Leiter, L.: Experimental Nephritic Edema, Arch. Int. Med. **48**:1 (July) 1931.

Kirk [21] and Shelburne and Egloff [22] found a relative or absolute increase in globulin in dogs with an experimental edema produced by plasmapheresis, and Leiter noted that the globulin increased much more quickly than the albumin when plasmapheresis was discontinued. Bruckman, D'Esopo and Peters [4] expressed the belief that the increase in globulin observed by them is coincidental, the result of such factors as syphilis or other infections, and stated that the changes in globulin cannot be correlated with the occurrence of edema. While this is undoubtedly true, in the sense that no relation of cause and effect between a lowered globulin content and edema can be demonstrated, our results show a distinct tendency toward an increased globulin with a lowered albumin content (chart 2) and a greater frequency of edema

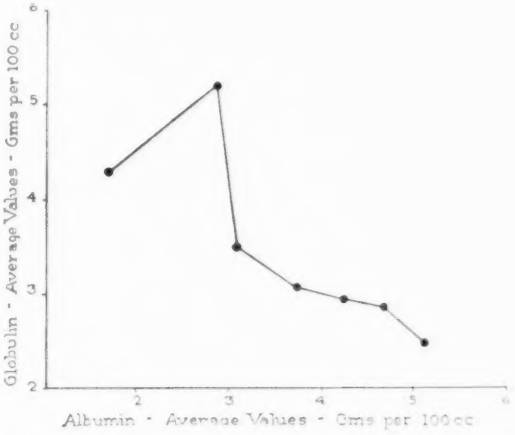


Chart 2.—In this chart the average values for each group of albumin determinations at intervals of 0.5 per cent (1.50-1.99, 2.00-2.49, etc.) have been determined, and the average values for the corresponding globulin determinations are plotted against them. The first point represents a single determination only. The tendency for the globulin to fall as the albumin values rise is evident.

among the cases with increased globulin. Our results and those of others suggest strongly that the increase in globulin in these cases is in the nature of a compensatory response which, however, often fails to prevent the occurrence of edema. Salvesen's case [23] has frequently

21. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

22. Shelburne, S. A., and Egloff, W. C.: Experimental Edema, Arch. Int. Med. **48**:51 (July) 1931.

23. Salvesen, H. A.: Hyperproteinemia in a Case of Nephrosis, Acta med. Scandinav. **45**:152, 1926.

been cited to show that globulin, though its osmotic pressure is lower, may, when present in sufficient concentration, prevent the formation of edema even in the presence of a very low albumin content. In our cases the increase in globulin was rarely sufficient to prevent entirely the formation of edema, but in several instances probably prevented the formation of much greater amounts. Weech and Ling found that when the globulin content was low, edema was almost always present and the albumin invariably deficient. The edema was considerably greater in their patients than in ours, and the protein concentrations were correspondingly lower. On the other hand, increases in globulin were greater and more frequent in our series. Although it is probable that the same cause is responsible for a globulin deficit as for albumin, it may be that the two fractions are unequally affected. It is suggested that the increase in globulin, though compensatory, is only possible in the milder or earlier stages of the disease or during the earlier stages of recovery.

The feeding of a diet of higher protein content was in a general way associated with an increase in the serum proteins and a lessening or disappearance of the edema, but the serum albumin did not rise to normal values for relatively long periods (six or eight weeks). This may have been due in part to an intake of protein lower than was advised. However, in Ling's patients on a diet of high protein content in the hospital, the serum albumin failed to reach normal over even longer periods, though the edema disappeared earlier. In contrast to Ling's findings the edema in our cases tended to persist until the albumin was well up to normal values. The difference between these two classes of patients and the influence of the factors discussed in relation to the edema and protein values are well illustrated by the two subjects of the studies of nitrogen balance. When confined to bed, with a resulting restriction of activity, both patients promptly lost the greater part of their edema (2.7 and 3.6 Kg., respectively) without any significant change in the serum proteins. Neither of these patients showed any marked gain in serum protein during her stay in the hospital in spite of a retention of nitrogen when placed on a diet of high protein content. The time, however, was much shorter than that necessary to raise the protein content to normal in the case of the outpatients. One patient was subsequently found to have a normal serum protein value and a complete loss of edema. The other could not be followed over a long enough period. The failure of the serum proteins to return to normal in relatively long periods, in spite of a high protein intake, is interesting. It is probable, since the serum proteins continued to increase for a long time, that nitrogen retention continued during the entire period, though neither our studies nor those

of others have been continued sufficiently long to demonstrate this. These observations suggest that in cases of nutritional edema the depleted nitrogen stores of the tissue are replenished before the serum proteins are greatly increased. On the other hand, in normal dogs made edematous by removing blood plasma (plasmapheresis), restoration of the serum protein may occur rather rapidly when an increased protein diet is fed,[22] and the possibility of some interference with regeneration of the serum protein in patients subjected to long-continued malnutrition must be considered. A few of the patients were given brewers' yeast for varying periods without a change in diet to determine whether an increased supply of vitamin B would influence the edema. In one or two of them there was a prompt rise in serum albumin. The protein content of the yeast was insufficient to account for the increase. The observations were too few and incomplete, however, to make the results more than slightly suggestive.

SUMMARY

Initial determinations of the serum proteins in thirty-one patients with nutritional edema and repeated observations in eleven of them, amounting in all to eighty-three determinations of total proteins and seventy-nine of serum albumin and globulin, are reported. In general, the total proteins were found to be normal, the serum albumin slightly or moderately reduced and the globulin normal or increased. Calculated colloid osmotic pressures were slightly or moderately below normal in the majority of patients with edema. When the protein in the diet was increased, the albumin tended to rise gradually, accompanied by a disappearance of the edema. However, this association was not exact, owing partly to a lag in the disappearance of the edema and partly perhaps to the influence of factors as yet not fully understood. Among the outpatients, irregularities of diet and infrequent observations may account for some of the discrepancies. In two cases, studies of nitrogen balance showed a retention of nitrogen on an increased protein intake. In one of these patients who was followed over a sufficient period there was an eventual rise in serum albumin to normal and a disappearance of the edema. The significance of these findings in relation to the edema is discussed.

DETECTION OF THE MURMUR OF ACUTE PERICARDITIS

DESCRIPTION OF A NEW CLINICAL PROCEDURE

HAROLD N. SEGALL, M.D.
MONTREAL, CANADA

Until the introduction of auscultation dry pericarditis was a disease only discovered on the post mortem table. The only evidence we have of its presence is the characteristic superficial to and fro murmur produced by movements of the heart. Its discovery is usually accidental and made when the heart is examined as a routine. There is no distinctive sign associated with it and in marked contrast to pleurisy it is essentially a painless complaint.
Sir James Mackenzie,[1] 1925.

The foregoing quotation reflects quite accurately the general attitude of physicians to the diagnosis of acute fibrinous pericarditis. Similar paragraphs may be found in most textbooks. In the most recent of the good monographs on heart disease, Dr. Paul D. White [2a] presented statistics which amply prove the opinions of Sir James Mackenzie. Dr. White said, "The characteristic sign of acute pericarditis, often found at some stage of the disease, is the friction rub, but in many cases (over 75 per cent) it is absent or escapes notice (Cabot 1926; a friction rub was heard in only 40, or 21 per cent of 186 cases of acute pericarditis)." It is indeed a common experience of clinicians to fail in detecting a pericardial friction murmur in cases which present an etiologic factor or symptoms suggesting pericarditis.

The salient features of the evolution of knowledge about the pericardial friction murmur offer some evidence which tends to explain these experiences. In a chapter devoted to the differential diagnosis of cardiac murmurs Laennec [3a] spoke of a *cri de cuir* sound which he said he at one time suspected of being a sign of pericarditis, but which he attributed to certain forms of exudative bronchitis. Laennec seems to have missed entirely the significance of this murmur, for although

---

From the Cardiac Clinic and the Medical Service of Dr. A. H. Gordon, the Montreal General Hospital, and the Department of Medicine, McGill University.

1. Mackenzie, James: Diseases of the Heart, New York, Oxford University Press, 1925.

2. White, P. D.: (*a*) Heart Disease, New York, The Macmillan Company, 1931, p. 509; (*b*) pp. 509 and 510.

3. Laennec, R. T. H.: (*a*) Traité de l'auscultation médiate et des maladies des poumons et du cœur, ed. 4, Paris, Masson & Cie, 1837, vol. 3, pp. 105 and 106; (*b*) p. 375.

Collin [4] described its association with three cases of pericarditis in 1824, no reference to these observations is found in the 1826 edition of Laennec's book. This may in part be due to the fact that both Laennec [4b] and his master, Corvisart,[5] taught that it was almost impossible to make a clinical diagnosis of pericarditis, and in part, also, to the uncertain tone in which Colin wrote of his observations. Of the three cases, he himself had studied only one. This patient presented a murmur analogous to the creaking (*craquement*) of new leather, which persisted for six days before signs of pericardial effusion developed; the patient died, but no autopsy was performed. The other two cases were described to Collin by Devilliers, a junior intern of Saint Antoine Hospital. Devilliers performed an autopsy in the second of these cases and found fibrinous pericarditis. From these observations Collin concluded that "Perhaps this murmur may be a constant sign of pericarditis before the development of pericardial serous effusion," and he attributed the murmur to pathologic dryness of the pericardium, which, moreover, he postulated as a characteristic of the initial stage of pericarditis. The first thorough clinicopathologic study of the auscultatory signs of pericarditis was made by William Stokes [6] (1834). This eminent clinician drew attention to the relative frequency of pericarditis, to the great variability in the quality and loudness of the friction murmur and to its frequent resemblance to other cardiac murmurs; he stated that though the murmur described by Collin is characteristic of pericarditis, it is the rarest of all the pericardial friction murmurs. In his book "The Diseases of the Heart" [7] (1854), Stokes alluded to the effect which posturing the patient has on the appearance and disappearance of the friction murmur, a fact first observed by Corrigan [8] (1842).

Because of the close resemblance between the protean forms of the pericardial friction murmur and endocardial and so-called functional murmurs, Stokes' observations have been ignored, and clinicians are inclined to depend on the discovery of the creaking, leathery, to-and-fro murmur for the diagnosis of pericarditis. Moreover, although Corrigan's observation suggests a method of eliciting the friction murmur, this procedure of changing the patient's posture is not reliable, since endocardial murmurs also vary with changes in the patient's posture.

4. Collin, V.: Des diverses méthodes d'exploration de la poitrine. Paris, J. B. Baillière, 1824.

5. Corvisart, J. N.: Essai sur les maladies et les lésions organiques du cœur et des gros vaisseaux, in Alibert, Bayle and others: Encyclopédie des sciences médicales, Paris, 1818, p. 1.

6. Stokes, William: Dublin J. M. Sc. **4**:29, 1833-1834.

7. Stokes, William: The Diseases of the Heart and Aorta. Philadelphia, Lindsay and Blakiston, 1854, p. 20.

8. Corrigan, D. J.: Proc. Path. Soc. Dublin, December, 1842.

The great frequency of cardiac murmurs of the endocardial type in rheumatic diseases, such as rheumatic fever and chorea, in cases of pneumonia and in septicemias and uremic states, militates against the discovery of pericarditis in such cases when the friction sound resembles an endocardial murmur. The lack of a satisfactory method of differentiating pericardial from endocardial murmurs has naturally led clinicians to consider all these murmurs as endocardial. Thus, one may conclude that the clinical diagnosis of fibrinous pericarditis is usually made only when the creaking, leathery, to-and-fro murmur arrests the attention of the observer.

My interest in the problem of eliciting the pericardial friction murmur, when it is not heard during an ordinary careful examination of the heart, and of differentiating it from other cardiac murmurs was aroused by the observations made in the following case.

REPORT OF A CASE

Observations Before Admission to Hospital.—A. F., a boy, aged 15, on Feb. 16, 1930, became rather acutely ill with pains in the abdomen as he got up in the morning; he had to return to bed after attempting to wash and dress. The abdominal pain persisted all day, and in the evening he vomited. During the next four days the abdominal discomfort continued as a rather bad ache with occasional severe exacerbations, and he was unable to retain any food, for he vomited soon after eating. He was able to retain water and orange juice. He was first observed by his physician, Dr. B. W. Segal, on February 20, when a moderate degree of fever, 102 F., and some generalized abdominal tenderness were found. When first seen by me in consultation with Dr. B. W. Segal on February 26, he still had the abdominal symptoms described, and, in addition, it was learned that deep breathing aggravated the abdominal pain and might cause vomiting, and that at times he had numbness or sensations of pins and needles in both hands and arms. On February 25, he began to notice some pain in the throat on swallowing and some pain in the left anterior part of the chest on taking a deep breath.

Past History: The patient had had measles, German measles, pneumonia, influenza and occasional colds as a small child. Tonsillectomy was done when he was 8 years of age. At 13 he had rheumatic fever, when he was ill for three months in the Royal Victoria Hospital and rested in a convalescent home for one month; a year later he had a mild recurrence, with illness for only two weeks. He did not recall having had any sore throat since the tonsillectomy.

Habits: The patient usually slept and ate well; the bowels were regular; there was no nocturia. He attended school from the age of 5 to 13, and since then, when not ill, had worked as a messenger.

Family History: The mother had died of a disease which caused dyspnea, in 1925; the father and three other children were alive and well; one younger sister had died of heart disease.

Physical Examination (February 26): The patient was a well developed and well nourished boy of 15, with a rather sallow complexion, who did not appear to be acutely ill. The body temperature was 102.6 F. The throat was acutely inflamed; there was some mucopurulent exudate on the posterior pharyngeal wall; there were very small tonsillar tissue remains from the tonsillectomy. The breath-

ing was rather rapid, 40 per minute, and shallow. Percussion resonance over the left base was somewhat impaired, and a few moist crackles were heard during inspiration at the base of the left lung posteriorly; no other abnormal pulmonary signs could be detected. The abdomen was tender all over, but most acutely in both flanks; the liver was palpable 1½ inches (3.77 cm.) below the right costal margin; no special area of rigidity of the abdominal wall could be defined. There was some tenderness in both costovertebral angles. The fundi presented somewhat engorged veins. No petechiae and no abnormalities of the skeletal muscles or joints could be detected.

Examination of the heart revealed the following: The apex impulse was 8 cm. from the midsternal line and 2 cm. to the left of the midclavicular line; a short presystolic thrill and a sharp systolic shock were felt at the apex; relative cardiac dulness was 2, 3.5, 6 and 8 cm. from the midsternal line in the second to fifth left interspaces and 3, 3 and 4 cm. in the second to fourth right interspaces. At the apex were heard a loud sharp first sound, a rather faint second sound and a decrescendo-crescendo diastolic murmur; the decrescendo phase was a short rumble which began a short time after the end of the second sound and faded completely; then after another brief interval the loud coarse crescendo phase began, and continued until it was interrupted by the loud sharp first sound. At the pulmonic area the first sound was short, dull and not loud; the second sound was loud and sharp and followed by a short diastolic "whiffy" murmur which began immediately after the end of the second sound; this murmur became louder as the stethoscope was moved downward along the left border of the sternum and was loudest and longest at the fourth space, where it occupied about half of the diastolic period and had a high-pitched blowing quality. At the aortic area and along the right border of the sternum the auscultatory signs were similar to those along the left border, but were less loud. No friction rub could be detected during ordinary auscultation, and it could not be elicited by a change in posture from the sitting to the recumbent positions, and vice versa. The blood pressure was 125 systolic and 60 diastolic; the heart rhythm was normal, and the rate was 100.

There was, of course, rheumatic heart disease, with mitral stenosis, aortic insufficiency, some left ventricular enlargement and apparently good cardiac function. However, no well defined cause for the symptoms and the fever could be determined; peritonitis, perhaps associated with acute appendicitis, recurrence of rheumatic fever or pneumonia, and pleurisy with referred abdominal pain were some of the possibilities to be considered. The patient was admitted to the Montreal General Hospital, in the medical service of Dr. A. H. Gordon.

Observations Made in the Hospital.[9]—The salient features of the examination on admission (Feb. 27, 1930), made by the junior intern, were as follows: an acetone odor of breath; perhaps some impairment of percussion resonance and bronchial breathing over the right base in the axillary region; slight bulging of the chest over the precordium; relative cardiac dulness 12 cm. from the midsternal line in the fifth left interspace; heart sounds loud at the apex, and "possibly a pericardial friction rub, heard best at the apex—this may be a mitral murmur. At base, second sound over aortic area is very sharp and distinct." There were tenderness and rigidity of the whole abdomen, most marked in the upper quadrants, and pain radiated into the loins. The liver was palpable 1 inch (2.5 cm.) below the costal margin in the midclavicular line. Pressure on the

9. Dr. A. H. Gordon and colleagues of both hospitals permitted me to abstract and quote their notes.

abdomen caused discomfort in the lower left side of the chest. There was a slight icteroid tinge over the face and the abdomen.

Electrocardiogram Taken on February 28: This showed sinus rhythm, with a rate of 100; a partial auriculoventricular block; P-R interval, 0.25 second; left axis deviation, with the P and T waves upright in all leads. The S-T interval was slightly above the base line in leads I and II. This record was considered to present evidence of active rheumatic myocarditis and relative enlargement of the left ventricle associated with aortic insufficiency, adherent pericardium or both.

Urine: The specific gravity was 1.022; the urine contained no sugar, albumin or casts (acetone ++ only on first day, and then absent).

Single X-Ray Plate of Chest (February 28): "Cardiac diameters show marked increase throughout. No evidence of any fluid in the pleural cavities. On the

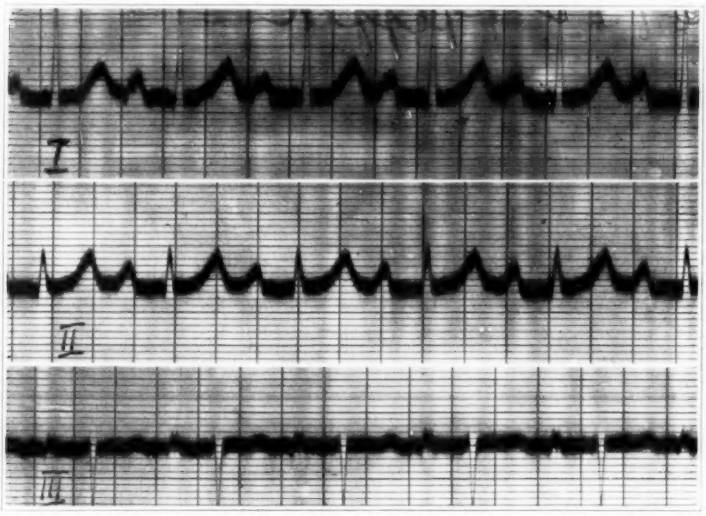


Fig. 1.—Electrocardiogram recorded on Feb. 28, 1930, showing partial auriculoventricular block: P-R interval, 0.25 second; rate, 100; left axis deviation; S-T interval, slightly above baseline in leads I and II.

left side in the sixth and seventh interspaces, extending from the cardiac shadow out to the axillary line, there is what appears to be some increase in density which might represent a small pneumonic process."

Examination of Blood (February 28): A count showed: red cells, 3,700,000; white cells, 23,800; hemoglobin, 70 per cent; polymorphonuclears, 88 per cent; basophils, 2 per cent; lymphocytes, 8 per cent; monocytes, 2 per cent. The platelets seemed increased and clumped. Chemical analysis of the blood showed: urea nitrogen, 13 mg.; creatinine, 1.7 mg. per hundred cubic centimeters, and sugar, 0.135 per cent.

Extracts of Clinical Notes Made by Dr. D. Mitchell, Senior House Officer, on March 1, in the Morning: The percussion note over the lungs was somewhat resonant except low in the left axillary region, where it was impaired; this had

been more pronounced the previous day. The breath sounds had been normal the previous day, but just at the outer border of cardiac dulness, there was a definite pleural friction; on this day this could not be heard. The relative cardiac dulness was 9 cm. from the midsternal line in the fifth left interspace. A presystolic murmur was heard at the apex; no thrill was felt. No other murmurs were heard. The impression was: rheumatic carditis, rheumatic pleurisy and decompensation.

Extracts of Clinical Notes by Dr. A. H. Gordon, on the Afternoon of March 1: The respirations were 36 per minute; the pulse rate, 96. There were a slight dulness of the percussion note and a slightly diminished loudness of the breath sounds over the base of the left lung. The heart was enlarged to the left, and auscultation at the apex revealed a canter rhythm of 3 beats, the first of which was the longest; no murmurs were heard. The abdomen was soft throughout, but tenderness was fairly diffuse and noticeably present in the right lower quadrant. The patient had coughed up a mass of blood-streaked mucopurulent sputum that did not resemble pneumonic sputum. The history of abdominal discomfort with the presence of definite tenderness was rather disturbing, but taken altogether the case suggested an atypical form of pneumonia.

A surgical opinion was requested, and on March 2, Dr. A. T. Bazin advised against immediate surgical intervention, although he could not rule out the possibility of acute appendicitis.

Clinical Notes by Dr. Gordon, March 3: "At apex there is a triple rhythm, a dash and two dots, with the dash systolic, and there is a short systolic murmur. At the base the first and second sounds are clear; immediately succeeding the second sound there is a soft rub; when this is followed downward it takes on a to-and-fro character, distinctly scratching in quality and not exactly coincident with the first or second sound. This is regarded as a pericardial friction rub."

Course: From February 27 to March 8, I failed to discover the pericardial friction murmur described, although the patient was observed at least once daily and occasionally two or three times. The auscultatory signs were consistently such as described when the patient was seen by me at his home. On March 8, during the usual attempts to elicit the friction murmur by changing the patient's posture, a loud to-and-fro *cri de cuir* type of pericardial murmur was heard all over the sternum during the time occupied by about a dozen heart beats; then it disappeared; several repetitions of the postural changes failed to elicit the murmur again. These experiences led me to think of the pathologic anatomy in this case. Visualizing the serofibrinous exudate, with just sufficient serum to separate the two layers of the pericardium, it occurred to me that by shaking the body of the patient, the heart might be caused to swing, somewhat in pendulum fashion, and thus the two layers of pericardium might be brought into contact for at least a sufficiently long period to elicit the friction murmur. With the patient in the dorsal recumbent position and the observer's hands on the chest in the axillary regions, the patient was shaken from side to side about half a dozen times in rather quick succession; on listening over the sternum immediately after this procedure, the loud friction murmur was heard again for about ten seconds, after which it disappeared. The shaking was repeated about a dozen times, and each time the murmur was heard during from ten to thirty seconds. From March 8 until March 20, the friction murmur remained audible. On ordinary auscultation, before shaking, it was heard on three occasions during this time. However, it could be elicited almost invariably after one shaking procedure, although sometimes only after two or three. A more gentle and equally effective method is to place the patient in the right lateral recumbent posture and have him move toward the

dorsal and prone postures, back and forth, several times. This procedure lends itself well in cases of adults, particularly heavy persons. The murmur was usually of the typical creaking, leathery, rubbing kind, but wide variations in loudness and quality were observed. Sometimes the systolic phase was loud, whereas the diastolic was barely audible, or the to-and-fro murmur had a soft swishing quality, and the elements varied in duration. At times the friction murmur resembled a systolic or a diastolic intracardiac murmur, from which it was distinguished only by its absence before shaking the patient and its disappearance after a few moments or minutes.

The patient remained in the hospital during ten weeks. Only occasional fleeting pains in the joints and muscles occurred to suggest rheumatic infection in the skeletal system. The main signs and symptoms were related to the pericardium and pleura (left pleural effusion); it is probable that the abdominal symptoms were, to some extent, due to rheumatic peritonitis as well as to pain referred from the inflamed serous surfaces above the diaphragm.

An interesting observation that offers additional evidence to prove the existence of pericardial effusion is the change in the electrical axis of the P waves and Q-R-S complexes which occurred in the first week. The appearance and disappearance of a small left pleural effusion were observed in three x-ray plates taken at intervals of several weeks. The x-ray plates did not aid remarkably in detecting or following the progress of the pericardial effusion. The size of the liver diminished gradually within the first three weeks, so that it was felt only at the costal margin on deep inspiration at about the time when it became impossible to elicit the pericardial friction murmur. The leukocyte count ranged between 23,000 and 10,000 during the first six weeks; a few days before the patient left the hospital it was 8,500. The temperature varied daily, usually between 99 and 102 F., during the first five weeks; then it gradually diminished, and for the next three weeks was between 97 and 99 F. For three days in the tenth week there was a rise again to 101, 100.4 and 99.6 F.; then the temperature resumed a relatively normal level. From the hospital the patient went to a convalescent home, where he remained for several months and then returned to light work. He has not had any illness in the past two years.

Abstract of Clinical History of Rheumatic Fever in the Royal Victoria Hospital from Feb. 26 to May 18, 1928.—The patient had been in normal good health until the afternoon of Feb. 22, 1928, when he began to feel ill; he noticed that on coughing or deep breathing he had a severe pain in the lower right side of the chest. The next morning the pain in the chest was less noticeable, but he had pain in the upper part of the abdomen, headache and vomiting. On the third day he felt more ill than ever; his throat felt sore, and he had pain all over the abdomen. One physician who saw him on this day prescribed rest and a milk diet. On the fourth day, another physician was called because the abdominal pain, vomiting and general sense of illness were worse, and he recommended the patient for admission to the surgical ward with a diagnosis of acute appendicitis. The salient features of the observations made by Dr. Webster, the intern in Dr. Keenan's service, were as follows: "Cheeks are flushed, patient does not appear to be in any great discomfort; throat is slightly red, breathing 26 per minute, pulse 130 per minute, temperature 102.6° F. Slight impairment of percussion resonance and some harshness of breath sounds over right lung base posteriorly. No pericardial or pleural friction rub. Heart sounds are too rapid to be analyzed. The abdomen is flat, moves freely with respiration; on light palpation the skin is hot, there is no rigidity and little if any tenderness; on deep palpation there appears to be generalized tenderness, especially in both kidney regions, anteriorly and

posteriorly. Liver and spleen are not palpable. White blood cell count 14,200. Urine, slight trace of albumin, otherwise negative." The patient was observed for four days by the surgeons; at no time did he appear acutely ill. Vomiting and abdominal pain were the chief symptoms until the third day, when he complained of pain and stiffness of the knee joints, and on the fourth day this latter symptom became the main source of discomfort. X-ray pictures of the chest and the abdomen were essentially negative. As the heart rate became slower, Dr. Webster noted "both sounds clear at apex" on the fourth day, and "heart examined, no abnormal findings" on the fifth day of the patient's stay in the surgical ward. Dr. Scriver was asked to see the patient and he found "presystolic, systolic and diastolic murmurs" over the heart; the patient was transferred to the medical service with a diagnosis of acute rheumatic fever on the fifth day after admission to the hospital.

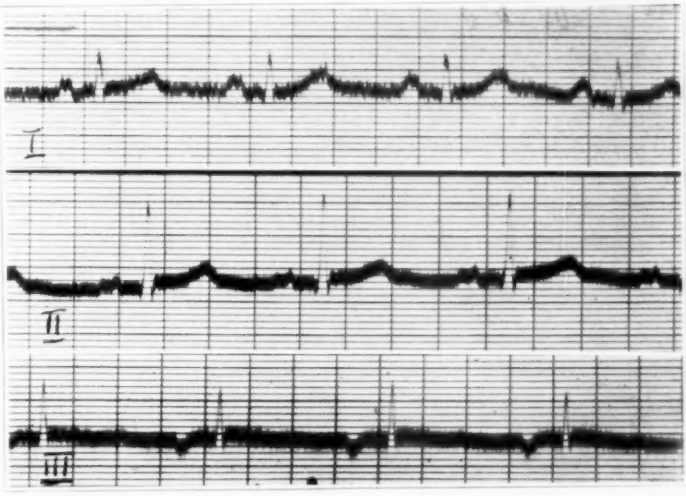


Fig. 2.—Electrocardiogram recorded on March 6, 1930. Note the shortening of the P-R interval to 0.20 second and the changes in direction and amplitude of all complexes as compared with the previous record. Left axis deviation of the P waves suggests enlargement of the left auricle associated with mitral stenosis.

The history, taken by the medical intern Dr. Jones, revealed that after two days of illness with general malaise, on the evening of February 22, the patient was suddenly seized with a stabbing pain in the chest, beneath the sternum, which lasted all night and prevented him from falling asleep. The next morning the pain in the chest was less severe, but he had crampy pains in the abdomen and vomited; the pain in the abdomen was diffuse but worse in the right lower quadrant. On the third day, some pain in both knees appeared, but the abdominal symptoms were the chief source of discomfort.

The patient recalled vaguely that he first began to have pain over the heart in 1925, and that in 1927 he began to notice shortness of breath on exertion.

He remained in the medical ward, in the service of Dr. J. Kaufmann, from March 2 to May 12, 1928; the illness had all the characteristics of rheumatic fever

with only a moderate degree of swelling of the joints; choreiform movements were noted occasionally; the electrocardiogram showed partial heart block with a P-R interval of 0.26 in the second of three records taken at intervals of several weeks. The heart murmurs were those of mitral stenosis and insufficiency and aortic insufficiency. The record contained frequent notes to the effect that a "friction rub was not heard." One notes, however, that auscultatory cardiac signs were differently described on different days by the same observers as well as by different observers.

COMMENT ON CLINICAL OBSERVATIONS

The two periods of illness, separated by an interval of two years, were similar in many respects. Both presented the problem of differential diagnosis between a surgical condition in the abdomen and a pathologic process above the diaphragm, to account for pain in the abdomen. The development of painful swollen joints was the first sign of rheumatic fever in 1928, whereas the almost accidental discovery of a friction rub on the fifth day after the patient's admission to the hospital in 1930 offered some positive evidence to account for the abdominal symptoms. The possibility of rheumatic peritonitis, indeed of rheumatic appendicitis, cannot be entirely ruled out for either of the illnesses. However, the history of pain in the chest at the onset of both illnesses and the observation of the pericardial friction murmur on numerous occasions, mainly with the aid of the shaking method, during the second illness makes it most likely that pericarditis occurred in both. The frequent references to the absence of a pericardial friction rub in the notes of the 1928 illness suggest strongly that this sign was consciously looked for, but apparently no special procedures were adopted in order to elicit it.

The history of this patient's experiences and of the difficulties in diagnosis which he presented to the physicians who saw him lends strong emphasis to the importance of detecting a pleural or a pericardial friction murmur.[10] Fussell and Kay [11] have described 3 cases of rheumatic pericarditis in children whose symptoms were those of acute appendicitis; in each instance the friction murmur was found at the first examination. A fourth case is mentioned in which the friction murmur was discovered immediately after the operation for appendectomy; the surgeon described the appendix as "mildly inflamed."

CHARACTERISTICS OF THE PERICARDIAL FRICTION MURMUR AND METHODS OF DETECTING IT

Collin was the first to suggest that the *cri de cuir* murmur might be a constant sign of pericarditis in its early stage; the authorities of his

10. Observations on the pleural friction murmur with the methods described in this communication are being collected and will be described in a future publication.

11. Fussell, M. H., and Kay, J. A.: Symptoms of Appendicitis in Acute Pericarditis, Am. J. M. Sc. **163**:40, 1922.

generation, Corvisart, Laennec and others, taught that pericarditis could not be diagnosed clinically. However, beginning with the work of William Stokes (1834), a long line [12] of keen students of clinical medicine have made numerous valuable contributions to the development of methods of investigation and of diagnostic thinking for the detection of pericarditis. A composite description of these contributions may be made in a few sentences and is to be found in the modern textbooks on heart disease. The *cri de cuir* murmur is indeed typical of the pericardial friction sound, but it is not a sine qua non to the diagnosis of fibrinous pericarditis. Short, soft to-and-fro murmurs, swishing to-and-fro or single murmurs and coarse or rasping murmurs, any of which may resemble some intracardiac or so-called functional murmur or may seem to be "close to the ear" and thus suggest pericarditis, have been heard and described in cases of acute fibrinous or serofibrinous pericarditis. Although the friction murmur is usually heard over a small area of the sternum, it may be restricted to any small area of the precordium or may be audible all over the area of relative cardiac dulness. It is extremely rare to hear it beyond the cardiac area, or over the back. By increasing the pressure with which the stethoscope is applied to the chest, the loudness of the murmur may be increased; by changing the posture of the patient, the loudness may also be varied. The pericardial friction murmur in any given case is apt to be unstable; it may appear and disappear like a jack-in-the-box; its loudness and quality may change remarkably, either gradually or with great suddenness. This instability is a valuable diagnostic feature.

Those who have written about the pericardial friction murmur have invariably adopted the point of view that is manifested in the foregoing paragraph. The discovery of a murmur is assumed, and ways and means of differentiating it are described. The general principle of these methods of distinguishing the murmur is similar to that of the methods used in differentiating various endocardial murmurs. Experience in recent years has made it clear that any general discussion of the pericardial friction murmur (and also of the pleural friction sound) should begin with, or should at least include, the description of methods for eliciting the murmur when it is not heard during the usual routine procedures of auscultation. As the mental attitude of clinicians to the

12. Hope, James: A Treatise on the Diseases of the Heart and Great Vessels, London, W. Kidd, 1832. Bouillaud, J. B.: Traité clinique des maladies du cœur, Brussels, H. Dumont, 1836. Skoda, J.: Abhandlung über Perkussion und Auskultation, Vienna, L. W. Seidel, 1839. Latham, P. M.: Diseases of the Heart, Philadelphia, E. Barrington & G. D. Haswell, 1847. Gibson, Francis: Pericarditis, in Reynold, J. R.: A System of Medicine, Philadelphia, J. B. Lippincott Company, 1877, vol. 4. Sansom, A. E.: Manual of the Physical Diagnosis of Diseases of the Heart, Philadelphia, P. Blakiston, 1881.

pericardial friction murmur will change from that of expecting it to arrest their attention to that of consciously searching for it with the aid of all known methods, fewer cases of acute pericarditis will escape them. The accumulated clinical and pathologic experience of various observers during the past century makes it possible to list the types of cases in which the existence of serofibrinous pericarditis should be suspected. A recent analysis by Gerke [13] of the etiology of pericarditis, based on the records of 26,771 postmortem examinations and 75,856 clinical case histories, offers valuable statistical data. These records represent observations made in three general hospitals and in one hospital for infectious diseases of Moscow (Russia) during the past twenty years. Pericarditis occurred most frequently in rheumatic infections: it was found at autopsy in 245 instances, and the clinical diagnosis was made in 91 cases which were not examined post mortem, these 336 cases represent 19.1 per cent of all the rheumatic cases. For tuberculous and pneumococcic infections, the incidence of pericarditis is 15.6 and 14.2 per cent, respectively; for nephritis it is 9 per cent; for infectious diseases (scarlet fever, measles, smallpox and diphtheria), 14.7 per cent, and for a variety of conditions—influenza, pyemia, myocardial infarction—20.6 per cent; there were 53 cases (2.5 per cent) in which no etiologic factor could be determined. White [2b] quoted a series of 244 cases of acute pericardial disease observed post mortem and reported by Preble (1901); pneumonia was the etiologic factor in 34 per cent, rheumatic fever in 28.4 per cent, nephritis (uremia) in 11 per cent, tuberculosis in 10 per cent, sepsis in 4.7 per cent, cardiac infarction and aneurysm of the heart or aorta in 2.6 per cent and typhoid fever in 1.7 per cent. He also referred to Stone's series (1919) of 300 cases of death from pneumonia in an army base hospital; 24 per cent of these showed acute pericarditis at autopsy. The presence of an etiologic factor for pericarditis is of more significance in arousing one's interest in discovering a friction murmur than the presence or absence of symptoms such as pain in the chest, cyanosis, dyspnea, tachypnea and abdominal symptoms, for pericarditis frequently exists without causing any such symptoms.

On analyzing the possible reasons for the instability of the pericardial friction murmur, there appear suggestions for clinical methods of eliciting it. The murmur is produced by the rubbing movement of the two pericardial surfaces lining the pericardial cavity, when fibrinous exudate is present on one or both of them. On the other hand, the murmur vanishes when these two layers are separated by fluid exudate or when the fibrinous exudate becomes sufficiently organized to cause fixed adhesion of the two layers of pericardium or when the organization

13. Gerke, A. A.: Die Ätiologie der Pericarditis, Virchows Arch. f. path. Anat. **278**:1, 1930.

and healing result in the smooth so-called milk patch. The separation of the two layers of pericardium by exudate may be only temporary, depending on the variations in the amount of fluid, as determined by the balance between exudation and resorption and by the disposition of the fluid in the pericardial sac. Thus, the murmur may appear, disappear and reappear. During these transitions, the quality, loudness and position of the murmur may vary. Following an attack of acute serofibrinous pericarditis there may remain a more or less close network of fibrous pericardial synechiae, enclosing spaces of normal pericardial surfaces; in a second attack of acute pericarditis the inflammatory lesions may be patchy in their distribution, and there may be different stages of the evolution of the pericarditis in the various spaces at different times. Such conditions would result in the permanent disappearance of a friction murmur over one area of precordium and its appearance over another. Moreover, in the small restricted spaces, variations in the amount and disposition of serum are apt to have a great effect on the character and the presence or absence of the murmur.

Curschmann [14] and, more recently, Conner [15] have drawn attention to anatomic features of the position of the heart within the chest which make it clear that even when large amounts of fluid are present in the pericardial sac, only a thin layer can exist between the two layers of pericardium on the anterior surface; because the heart lies quite snugly interposed between the sternum and the spinal column, pericardial effusions accumulate laterally. Conner, therefore, emphasized the fact that the accumulation of a large amount of pericardial effusion does not necessarily imply the disappearance of the friction murmur, and he described observations which prove this to be true. Thus, whether the pericardial effusion accompanying the fibrinous exudate is large or small and whether the area of pericarditis is small or widespread, the pericardial friction murmur may be observed to appear and disappear as long as there is fibrinous exudate on one or both surfaces, at or near the anterior aspect of the heart. Under such conditions, any procedures that will cause the separated inflamed surfaces to be brought into contact with one another will be effective in eliciting the murmur.

It is well known that under normal conditions the position of the heart in the chest cavity changes appreciably during deep respiration and with variations in posture. The heart may be said to be suspended from the inferior and superior venae cavae and the arteries which leave the arch of the aorta to go to the head. Consequently, with changes in posture or variations in the height of the diaphragm, the heart swings or

14. Curschmann, H.: Deutsche Klin. **15**:401, 1907.

15. Conner, L. A.: On the Diagnosis of Pericardial Effusion, Am. Heart J. **1**:421, 1926.

rotates around this axis. Under normal conditions, the negative pressure in the chest causes a fixed relation between the two layers of pericardium so that the parietal layer moves *pari passu* with the heart, as the position of the heart alters during changes in posture of the body or during movements of the diaphragm. When there is a pericardial effusion, the difference in the specific gravity of the fluid and of the heart makes it possible for the heart to move over a greater arc than the parietal pericardium; the heart, being heavier, will displace fluid in an upward direction. Because the heart fits in so closely between the sternum and the spinal column, little movement in the anteroposterior direction can occur. On the other hand, both because the bulk of fluid accumulates on the lateral aspects of the heart and because the lungs are compressible, the heart moves much more freely from side to side. It is mainly the movement of the heart within the pericardial cavity that causes changes in the disposition of the fluid exudate and brings about the instability of the pericardial friction murmur. Thus, the same procedures that may help to elicit the murmur may cause it to disappear. This phenomenon lends itself very well for use as a test to differentiate the friction from other cardiac murmurs.

The procedure of shaking the chest, which proved so successful in the case described, is but one of the many methods of altering the position of the heart. It seems, however, to have certain advantages which under suitable circumstances make it the method of choice. The simpler methods may be tried: 1. Deep breathing, coughing, sighing, yawning and sneezing, chiefly in virtue of the movements of the diaphragm, cause changes in the lie of the heart which may affect the presence or absence of a pericardial friction murmur. 2. A second group of procedures consists of changes in the posture of the patient, performed slowly or rapidly; the greatest amount of movement of the heart will take place during a shift from one lateral recumbent position to the other. Closely related to the shaking procedure is voluntary movement of the patient from side to side as he occupies the knee-chest position, or from the dorsal to the prone position as he lies on one side. This last procedure is a relatively gentle and effective one; it is suitable for the observation of rather heavy persons and is applicable to sick patients in whom it can be carried out at a slow rate, the patient being entirely passive. Another postural change that merits being mentioned is that from the recumbent to the sitting posture; Corrigan observed the appearance and disappearance of the pericardial friction murmur with this procedure in 1842. The various respiratory and postural movements may be combined; thus, deep respiration in the knee-chest position is likely to elicit the murmur, to alter its character and location or to cause it to vanish.

When the murmur is of the typical to-and-fro, leathery, creaking type it leaves no doubt as to the existence of pericarditis. But it may resemble any of the endocardial or exocardial murmurs, which also vary with respiratory and postural changes, so that other differentiating characters become necessary. Perhaps the most important of these is the transitory nature of the pericardial murmur, which is elicited by any of the foregoing procedures. It is likely to be heard for only a few moments or minutes, and repeated maneuvers may be required to elicit it again. The same procedure that caused the murmur to appear may cause it to vanish. It may be heard after one procedure at a given time, and only after another procedure at another time. On the other hand, the murmurs from which it must be differentiated have a constant relation to the postures in which they are present or absent; if one of these murmurs is audible only in the recumbent posture, it persists as long as the patient maintains this posture, and this may be readily observed at any time in the course of days or months. The friction murmur that is elicited repeatedly by the same or different procedures may vary in quality, in loudness and in position each time it is heard, whereas for the other murmurs these characters are quite constant.

On a priori grounds, conditions that would prevent variations in the friction murmur must be recognized. Thus, given a certain degree of organization with fibrous adhesion in the midst of an area of fibrinous exudate, the two layers of pericardium would be sufficiently fixed at this point to make it impossible to separate them enough to cause the murmur to vanish, or perhaps even to alter its loudness or quality. Under such circumstances, the friction murmur is to be heard with equal loudness and at the same point in all postures and after shaking. It disappears only when the process of fibrosis and fixed adhesion is completed. One would, however, most likely find that the friction murmur over other portions of the precordium would vary with different procedures which alter it when there are no fibrous synechiae.

Whereas the respiratory and postural movements seem simpler procedures than that of shaking or rolling the patient's body, the latter have a number of advantages which make them the methods of choice: (1) By shaking or rolling the heart is moved rather quickly in many directions; (2) it is much less fatiguing for the patient to be moved passively than to perform a series of voluntary movements; (3) in differentiating the friction murmur from other murmurs, the elements of change in posture and respiratory phase which affect these murmurs are eliminated, for auscultation is carried out under the same conditions before and after shaking or rolling. It has repeatedly been observed that after the pericardial friction murmur has been elicited by a given change in posture, it may be caused to vanish or reappear or to change in loudness, quality and position by the shaking method. In cases of

repeated pericarditis the acute inflammation is limited to spaces bounded by the fibrous adhesions resulting from previous attacks; the heart does not move sufficiently with changes in posture or during respiratory variations to affect the conditions that determine the presence or absence of a pericardial friction murmur. The case reported is an example of this type of condition, in which the shaking method is the most effective in eliciting the murmur.

CONCLUSIONS

The pericardial friction murmur is a clinical sign the detection of which depends on methods of eliciting it and of differentiating it from other murmurs that may be heard over the precordium. From the point of view of the observer in search of clinical signs the discovery of a typical leathery friction rub in the course of an ordinary examination of the heart may be looked on as a fortunate accident.

Respiratory movements, postural changes and shaking or rolling of the body may cause a pericardial friction murmur to appear, to vanish and to reappear, and they may alter the loudness, quality and position of the murmur. These procedures, therefore, constitute methods of eliciting a friction murmur and of differentiating it from other murmurs which it may resemble.

ACUTE LEUKEMIA FOLLOWING LYMPHOSARCOMA

KATSUJI KATO, PH.D., M.D.
AND
ALEXANDER BRUNSCHWIG, M.D.
CHICAGO

Lymphosarcoma and lymphatic leukemia have been regarded as two distinct pathologic conditions. In recent years, however, the leukemic state has come to be regarded as merely a phase of circulating metastases from lymphosarcoma. This implies that all patients with leukemia present the condition of lymphosarcoma earlier in their histories, and that this condition may not have been clinically evident because of the deep location of the involved lymph nodes.

A review of the entire literature for the presentation of evidence proving the correctness of the hypothesis stated is beyond the scope of this report. However, attention may be called to the more recent reports which deal with cases similar to the ones we present.

Evans and Leucutia,[1] in 1926, treated sixteen patients who had lymphosarcoma with deep roentgen therapy; all showed a uniformly rapid subsidence of symptoms. The exact dosage employed in these cases is not stated by the authors, but usually after from five to ten therapeutic exposures, the sarcomatous swellings disappeared and the general condition of the patients so improved that they were permitted to resume their respective occupations. This same degree of radiosensitivity was also seen in the leukemic cells in the circulating blood, for their number promptly dropped if the therapy was applied at the time of a high lymphocyte count.

Among the sixteen patients so treated, however, there were three young adults who in from one to three months after their discharge returned to the hospital with the typical clinical picture of acute lymphatic leukemia, which progressed rapidly to a fatal termination. Similar cases with an identical clinical and therapeutic course were first described by Wagner[2] and by Webster[3] in 1920. Other cases of

From the Departments of Pediatrics and of Surgery, the University of Chicago.

1. Evans, W. A., and Leucutia, T.: The Neoplastic Nature of Lymphatic Leukemia and Its Relation to Lymphosarcoma, Am. J. Roentgenol. **15**:497 (June) 1926.

2. Wagner, R.: Leucosarcomatose (Sternberg), Wien. med. Wchnschr. **70**: 1655, 1920.

3. Webster, L. T.: Lymphosarcoma, Lymphatic Leukemia, Leucosarcoma, Hodgkin's Disease, Bull. Johns Hopkins Hosp. **31**:458, 1920; Johns Hopkins Hosp. Rep. **20**:251, 1921.

TABLE 1.—*Cases of Leukemia Following Lymphosarcoma*

Author, Year	Sex, Age	Origin	Blood Picture at Outset	Therapy	Effect of Therapy	Development of Leukemia	Autopsy: Final Diagnosis
Wagner, 1920	Male, 5 years	General lymphadenopathy with mediastinal tumor	Normal, but large lymphocytes predominated	3 daily exposures, 5 later	Disappearance of lymphadenopathy	6 weeks; white cells, 360,000 (small lymphocytes)	Leukosarcoma
Webster, 1921	Male, 28 years	Localized tumor of the chest	Normal; white cells, 3,900	Half an hour daily for 10 days	Leukemia; white cells, 31,000, with ecchymoses	Immediately after treatment	No record
Evans and Leucutia, 1926	(1) Male, 25 years	Mediastinal gland	Normal; white cells, 14,100 (polymorphonuclears 72%)	Irradiation for 10 days	Disappearance of tumor; white cells, 2,200	1 month; metastatic nodules on scalp; white cells, 144,000	Lymphosarcoma, with marked changes in marrow
	(2) male, 15 years	Mediastinal gland	Normal; white cells, 12,500 (polymorphonuclears 64%)	Irradiation for 10 days	Rapid improvement; white cells, 200	5 months; pain in legs, mass in left testicle; white cells, 300,000	None
	(3) Male, 21 years	Generalized lymphadenopathy	Normal; white cells, 8,600 (polymorphonuclears 78%)	Irradiation	Improvement; white cells, 600	5 months; numerous nodules of the skin; white cells, 84,000	Lymphosarcoma of lymph gland and bone marrow
Borchardt, 1927	Male, 43 years	Mediastinal gland	Normal	Irradiation	Improvement; white cells, 6,800	7 months; white cells, 100,800 (lymphocytes 98%)	Lymphatic leukemia
Kneal, 1927	Male, 7 years	Mediastinal mass	White cells, 12,600 (polymorphonuclears 82%)	Several roentgen ray exposures	Decrease of mass in 1 month	1 month; hemorrhage and pallor; white cells, 531,000 (lymphocytes 80%)	No record
Young and Spalding, 1928	Male, 8 years	Mediastinal gland	White cells, 22,000 (polymorphonuclears 56%)	Irradiation	White cells, 1,016,000 (lymphocytes 93%)	2 weeks	Mediastinal lymphosarcoma
Hensel, 1928	Male, 15 years	Mediastinal tumor	White cells, 13,000 (polymorphonuclears 58%)	Irradiation	White cells, 832,000 (lymphocytes 92%)	Several months	Lymphosarcoma (thymus)
Flashman and Leopold, 1929	Male, 60 years	Inguinal gland	Slight lymphemia; white cells, 7,300	3 weekly for 4 months	Improvement; white cells, 5,000 and 7,000	4 months; white cells, 96,000 (lymphocytes 90%)	
Landau, 1930	Male, 5 years	Generalized lymphadenopathy mediastinal tumor and left pleural exudate	Normal; white cells, 13,200	Roentgen rays	Marked improvement; white cells, 5,100	1 month; white cells, 56,000 (lymphocytes 87%)	Lymphosarcoma; leukemia metastases
Cooke, 1932	(1) Male, 12 years	Mediastinal tumor	Normal; white cells, 9,200 (polymorphonuclears 71%)	5 daily exposures	Marked improvement; white cells, 6,200	6 weeks; white cells, 110,000 (lymphocytes 98%)	None
	(2) Male, 5 years	Mediastinal glands	Normal; white cells, 12,200 (polymorphonuclears 61%)	5 daily irradiations	Disappearance of enlargement	5 weeks; recurrence of enlargement and ecchymoses; white cells, 33,000 (lymphocytes 95%)	None
	(3) Male, 5 years	Mediastinal gland	Normal	2 days irradiation	Disappearance of signs, but mass persisted; white cells, 8,400	2 months; white cells, 35,200 (lymphocytes 92%)	None
	(4) Male, 3.5 years	Mediastinal gland	Normal	4 days; white cells, 21,400 (polymorphonuclears 56%), no abnormal cells	Disappearance of mass; white cells, 2,100 (polymorphonuclears 75%)	2 months; white cells, 317,000	None

lymphosarcoma terminating in leukemia after deep roentgen treatments have been reported by Borchardt,[4] Kneal,[5] Young and Spalding,[6] Hensel,[7] Flashman and Leopold[8] and Landau.[9] Recently Cooke[10] collected from the literature seventy-four cases of mediastinal tumors associated with leukemia and reported several similar cases of his own. Four of the patients came under his observation in the "preleukemic" stage, but after the institution of roentgen irradiation, terminal leukemia developed in all. The summary of the cases previously reported is given in table 1.

In the light of the preceding brief review of the literature, the two cases herein presented are of special interest, in that the same combination of symptoms and course is illustrated.

Fig. 1.—Photograph of patient, M. K., taken on first admission to hospital in January, 1932, showing the swelling of the left parotid and cervical regions.

REPORT OF CASES

CASE 1.—*History.*—M. K., a 5 year old girl, came to the University of Chicago Clinics on Jan. 7, 1932, with the complaint of swelling of the left side of the face (fig. 1). The swelling began to appear insidiously six months prior to presenta-

4. Borchardt, H.: Beitrag zur Frage der Gewächse mit leukämischen Blutbild, Verhandl. d. deutsch. path. Gesellsch. **22**:96, 1927.

5. Kneal, E.: A Case of Lymphatic Leukemia, Am. J. Dis. Child. **33**:541 (March) 1927.

6. Young, G. J., and Spalding, J. E.: Report on a Case of Lymphosarcoma of Thymic Origin with Acute Lymphoid Leukemia, J. M. Soc. New Jersey **25**:609, 1928.

7. Hensel, O.: A Case of Leukosarcomatosis, M. J. & Rec. **128**:528, 1928.

8. Flashman, D. H., and Leopold, S. S.: Leukosarcoma, with Report of a Case Beginning with a Primary Retroperitoneal Lymphosarcoma and Terminating with Leukemia, Am. J. M. Sc. **177**:651, 1929.

9. Landau, A.: Ein Fall von Lymphosarkom mit terminalem leukämischen Blutbild, Ztschr. f. Kinderh. **48**:614, 1930.

10. Cooke, J. V.: Mediastinal Tumor in Acute Leukemia, Am. J. Dis. Child. **44**:1153 (Dec.) 1932.

tion. There was no sore throat, coryza, earache, cough or fever at any time preceding or during the development of the swelling. Tonsillectomy had been performed three months previously, but no change in the size of the swelling was noticed. The swelling was not painful but it was tender to pressure. The patient had been up and about and not confined to bed at any time. The swelling was apparently quite different in nature from a similar swelling on the opposite side which had developed two years previously, and which was satisfactorily treated by incision and drainage. Otherwise, the patient's past history was irrelevant, and there was nothing of consequence in the family history.

Examination.—Physical examination revealed a well developed but poorly nourished white girl, not acutely ill. The positive findings were: (1) a large swelling

TABLE 2.—*Blood Picture in Case 1*

Date	Red Cells, Millions	Hemoglobin (Sahli and Newcomer) per Cent	White Cells	Platelets	Differential					Reticulocytes, per Cent
					Lymphocytes	Polymorphonuclears	Mononuclears	Eosinophils	Basophils	
1/ 8/32	5.30	98	6,200	.....	26	72	2	0	0	...
1/17/32	5.70	11.2	4,500	320,000	16	79	4	1	0	0.9
2/22/32	2.74	5.1	179,200	28,000	98	2	0	0	0	...
2/23/32	....	....	.....	.....	93	3	2	1	1	...
2/29/32	0.90	4.5	18,000	20,000	94	4	0	1	1	...

TABLE 3.—*Roentgen Treatment in Case 1**

Date	Area Exposed, Diameter	Area Treated	Dosage (Air Value), Roentgens
1/11/32	15 cm.	Left cervical and submaxillary glands	412.5
1/12/32	.....	Left cervical and submaxillary glands	137.5
1/13/32	10 cm.	Anterior left axilla	206.0
	10 cm.	Anterior right axilla	206.0
1/14/32	10 cm.	Anterior left axilla	206.0
	10 cm.	Anterior right axilla	206.0
1/15/32	20 cm.	Both inguinal glands anteriorly	206.0
1/16/32	15 cm.	Anterior thorax (for mediastinum)	275.0
1/18/32	10 cm.	Left cervical and submaxillary glands	206.0

* The patient was treated at the University of Chicago Clinics. The tube was impressed with 150 kilovolts peak (sphere gap). The filter used was 0.25 mm. of copper plus 1 mm. of aluminum; the effective wave length, 0.187 angstroms, and the focus skin distance, 50 cm.

over the parotid area on the left side of the face, involving the upper third of the neck; it was firm, hard, most prominent at the angle of the jaw and not tender or fluctuating; (2) a firm mass measuring 2 by 1.5 cm. in the submental region; (3) a slight enlargement of the postauricular glands; (4) swollen ampulla of the left Stenson's duct; (5) a hyperemic pharynx, and (6) moderate malnutrition. Roentgen examination of the region of the neck and of the chest did not show a pathologic condition of the bones or lungs, and the blood picture was entirely normal, as is shown in table 2.

Two days after admission, biopsy of the large tumor of the left parotid region revealed a heavy invasion of uniform-appearing lymphoblasts obviously not far removed from the normal lymphocytes. The pathologic diagnosis was lymphoblastoma (of the Paltauf type) which had broken through the capsule and infiltrated the surrounding tissues (fig. 2). Under an oil immersion lens, the lymphoblasts showed evidence of active proliferation, as each field contained from two to five mitotic figures (fig. 3).

Treatment and Course.—The therapeutic measures adopted were saturation therapy at two day intervals of the lymph nodes of the left cervical region and generalized irradiation of other lymphatic areas. The irradiation was carried on under the supervision of Dr. Charles S. Capp of the department of roentgenology, and the technical details are given in table 3.

The blood count made at the conclusion of the treatment showed again a normal picture, with, however, decided leukopenia and a normal differential count.

As a result of the roentgen therapy, the tumor mass on the left side of the face disappeared almost completely, and the patient was discharged.

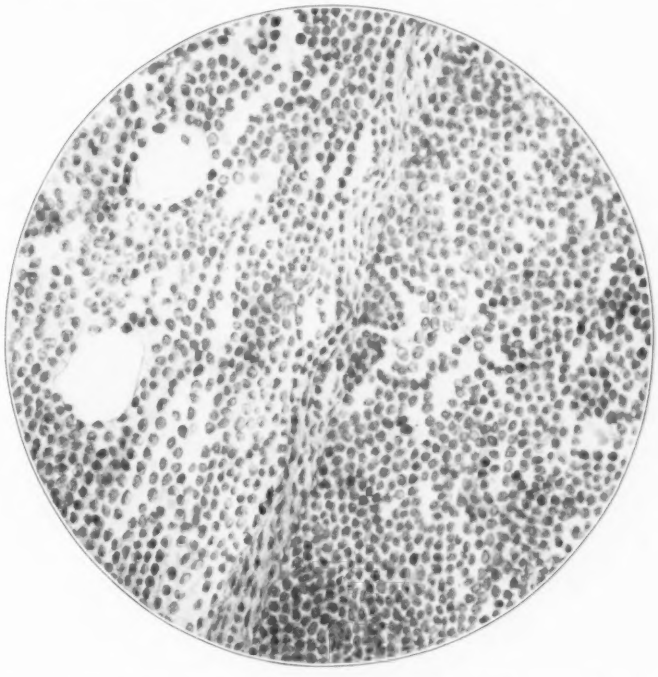


Fig. 2.—Histologic specimen of the cervical lymph gland removed at biopsy, Jan. 9, 1932. The parenchyma of the gland is a mass of proliferating lymphoblasts which have invaded the extracapsular areolar tissue, with thinning of the capsule. The section was embedded in paraffin and stained with hematoxylin and eosin. The drawing was made with camera lucida, a 4 mm. objective and 5 × ocular being used.

The patient remained well for about four weeks; at this time her parents again noticed the swelling at the same place. It grew for two days. They further noticed that the child would easily acquire black and blue marks and that there was bleeding from the nose and mouth. The appetite began to fail, and a slight rise in temperature was also noted. The mother found one day that the child's urine was blood-tinged. The patient was readmitted to the hospital, and physical

examination revealed: (1) signs of hemorrhages from nose and mouth, (2) purpuric spots in various parts of the body, (3) enlarged cervical glands, (4) palpable spleen, (5) hematuria and (6) prolonged bleeding time.

Examination of the blood disclosed the true nature of the disease, as is seen in table 2. The tissue culture of the blood cells was made by Dr. William Bloom of the department of anatomy, who stated that the predominating cells did not show active tendencies to differentiate into myeloid types, a fact which supported the assumption that they were lymphocytic.

After a transfusion of blood had been made, the patient was discharged, against advice. One week later, the child was brought to the hospital for the third time.

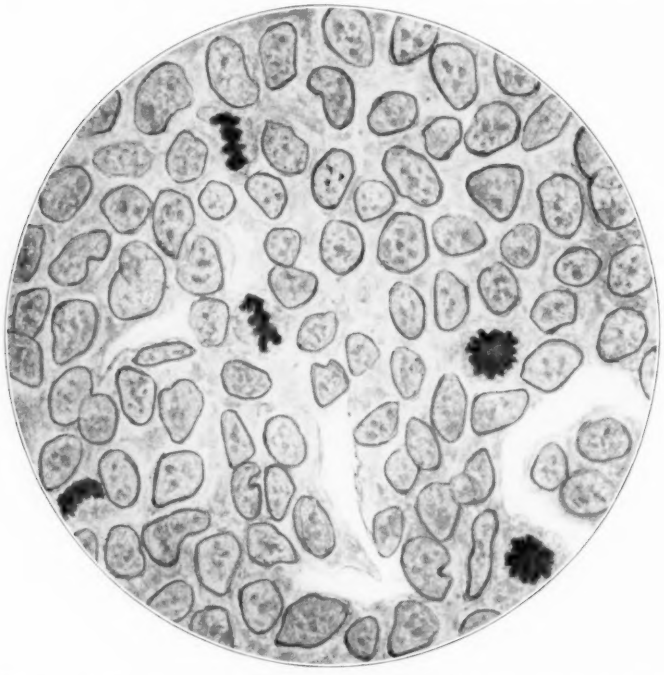


Fig. 3.—A portion of the parenchyma of the lymph gland shown in figure 2, seen under an oil immersion lens, 1.9 mm., with 10 × ocular, showing five mitotic figures in the field.

She had been failing steadily and was found to be moribund. Ecchymotic areas were multiplied over the entire body. The spleen and the liver were large. Examination of the blood showed a general reduction in the number of both the red and the white cells. Another transfusion was given, but the patient continued to be lethargic. She died on the third day after admission.

Autopsy.—At autopsy, which was performed by Dr. Eleanor M. Humphreys of the department of pathology, the most striking picture was that of the numerous petechial hemorrhages found over the surfaces of the heart and the lungs (fig. 4).

Fig. 4.—The heart and the lungs of the patient in case 1, removed at autopsy on March 2, 1932, by Dr. E. M. Humphreys, showing numerous petechial hemorrhages over the surfaces of the organs.

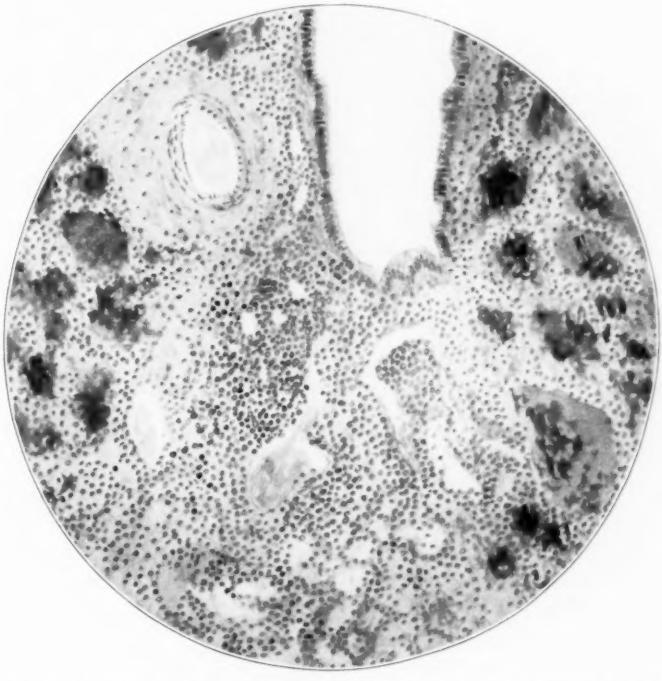


Fig. 5.—A section of the lung in case 1, showing a moderate amount of lymphocytic infiltration around a bronchiole, together with hemorrhagic infarcts and coagulation necrosis. The section was embedded in celloidin and stained with hematoxylin and eosin. Camera lucida drawing, with a 4 mm. objective and 5 × ocular.

The purpuric spots were also found on the skin in general, but were particularly marked over the extremities. There were also extensive submucosal hemorrhages in the pelves and the calyces of both kidneys, which extended down to, and stopped sharply at, the ureteropelvic junctures. Microscopically, contrary to our expectations, the sections of various organs showed a rather scanty evidence of lymphocytic infiltration. The only evidence consisted of the slight infiltration around some of the bronchioles in the lungs (fig. 5) and a slight hyperplasia of the lymphoid elements in the intestinal mucosa (fig. 6). The spleen showed only moderate hyperplasia and the liver, extensive central necrosis involving practically all

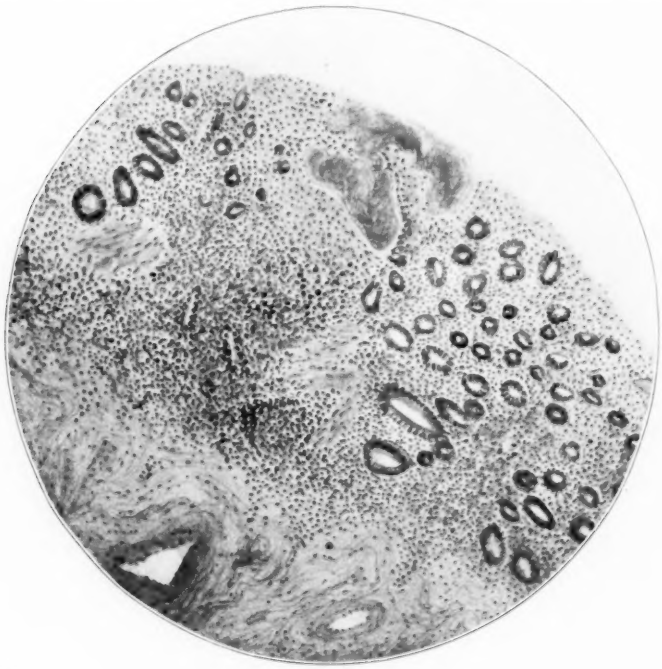


Fig. 6.—A section of the large intestine, showing a slightly abnormal lymphocytic infiltration of the mucosa, with a small necrosis on the surface. A celloidin section, stained with hematoxylin and eosin. Camera lucida drawing, with a 4 mm. objective and 5 × ocular.

of the lobules, without, however, any inflammatory reaction. In the kidneys was found a scattered area in the interstitial tissue which contained pyknotic and fragmenting nuclei, again without any inflammatory changes. The bone marrow was edematous and rather scanty in the myeloblasts and erythroblasts. The presence of mycotic emboli in the lungs and in some lymph nodes was also noted. Many healing encapsulated tubercles were also found in various organs.

Case 2.—*History.*—A. S., a 9 year old boy of Polish parentage, entered the Children's Memorial Hospital on Aug. 31, 1931, with a complaint of difficulty in

breathing and spells of choking. His mother stated that about one month previously he had complained of headache, abdominal pain and, especially, a feeling of pressure under the sternum. He coughed frequently, slept restlessly and ate poorly. He had lost 8 pounds (3,600 Gm.) during the month prior to admission.

The past history indicated that he had never been robust. He was a full term baby. The labor was difficult, and terminated with a version and extraction. The right humerus was fractured at delivery, and an injury to the cervical nerves occurred, producing an Erb's palsy. When the patient was 13 months of age, he was operated on in an attempt to repair the injury done to the arm at birth. This operation was only partially successful, as he suffered trophic disturbances in the skin of the hand and arm at various times.

Examination.—Physical examination revealed a poorly nourished and developed boy who breathed with considerable difficulty (fig. 7). The tonsils were slightly injected but not markedly enlarged. The anterior and posterior cervical lymph

Fig. 7.—Photographs of the patient, A. S., taken at various stages of the disease: 7 *A*, taken on Sept. 1, 1931, shows the tumor mass over the upper part of the anterior portion of the wall of the chest; 7 *B*, taken on September 29, shows bilateral cervical enlargement. About this time the hospital record shows a rise in temperature to 104 F., which persisted until death on October 14. In 7 *C*, taken also on September 29, numerous purpuric spots over the lower extremities are shown.

nodes were pea-sized. The trachea and larynx were displaced to the right of the midline by a mass which bulged out into the left supraclavicular region, and which was continuous with a nodular swelling projecting 1.5 cm. above the wall of the chest and measuring 4 cm. in diameter in the left infraclavicular region. The superficial veins of the chest and abdomen were distended. The respiratory excursions of the left thoracic wall were definitely limited, and the percussion note was dull over the left side of the chest anteriorly and posteriorly. Over the upper part of the lungs, the breath sounds were tubular, and below the angle of the scapula they were suppressed. The right lung was hyperresonant and the breath sounds exaggerated. The heart was displaced to the right, the point of maximum impulse being in the fifth interspace just to the right of the sternum. The tones were

muffled and distant, but no murmur was heard. The liver was palpable two finger-breadths below the costal margin; no other masses were palpable in the abdomen. The left arm and the legs were normal. The inguinal, axillary and epitrochlear lymph nodes were not enlarged.

The urine showed a trace of albumin. The blood counts made at various stages of the disease are summarized in table 5.

The roentgenograms (fig. 8*A*) showed a wide, dense mediastinal shadow measuring 11 cm. in width and extending from the second thoracic vertebra to the diaphragm. This shadow could not be separated from the shadow of the heart, and was thought to be due to a mass of tumor glands. A slight clouding of the upper two lobes of the left lung and dense clouding of the lower lobe were thought to be caused by a partial atelectasis due to compression by the tumor mass.

Diagnosis.—At this time a diagnosis of mediastinal tumor was made and deep roentgen therapy was instituted at Grant Hospital, as shown in table 4. After the third treatment, the appearance of the patient was quite different from that noted

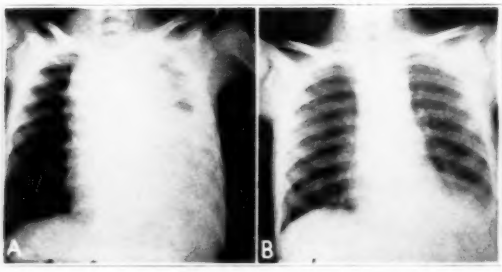


Fig. 8.—Roentgenograms of the chest in case 2: *A*, taken on Aug. 29, 1931, shows the mediastinal tumor mass with left pleural exudate, and *B* (taken on September 9, after a course of deep roentgen treatments) shows the disappearance of the tumor and of the exudate.

TABLE 4.—*Roentgen Treatment in Case 2**

Date	Kilo-Voltage	Area Treated	Dosage in Milliampere Minutes
9/3/31	130	Anterior left part of the chest and mediastinum	175
9/4/31	130	Anterior left part of chest and mediastinum	100
9/5/31	140	Posterior left part of chest and mediastinum	100
9/8/31	140	Posterior left part of chest and mediastinum	125
9/9/31	140	Posterior left part of chest and mediastinum	50
	140	Anterior left part of chest and mediastinum	75

Patient was instructed to return in one month for further treatment.

* The patient was treated at the Grant Hospital, Chicago. The voltage of the tube was determined by a calibrated spherical gap. A filter of 0.25 mm. of copper plus 1 mm. of aluminum was employed. The focal skin distance was 50 cm.; the area of exposure, 20 cm. square.

at the time of entrance. He breathed more easily and had lost his appearance of anxiety, and percussion of the chest revealed that the tumor mass had become definitely reduced. After the fourth treatment, the respiratory excursions of the lungs were equal, and the breath sounds over the chest, anteriorly and posteriorly, were normal. An area of dulness extended 1 cm. to the right and 2 cm. to the

left of the sternum in the first and second interspaces anteriorly and to about 2 cm. to either side of the upper thoracic part of the spine posteriorly. The heart was still displaced to the right. The roentgenograms showed that the left lung was entirely clear, except for a slight clouding at the cardiohepatic angle. The width of the mediastinal shadow was one half of that observed in the first roentgenogram (fig. 8*B*).

The patient was discharged with instructions to return in one month for a follow-up examination.

Second Admission.—Thirteen days after discharge he was brought to the dispensary with a history of having been well until four days previously, when he began to be feverish and to have difficulty in breathing again. He had had recent nosebleeds, and blue spots had appeared in the skin. The mother had noticed an enlarging swelling on either side of the neck for three days.

On physical examination it was noted that the child was much thinner than at the time of the previous admission. Numerous petechiae and raised purpuric areas

TABLE 5.—*Blood Picture in Case 2*

Date	Red Cells, Millions	Hemoglobin, per Cent (Sahli)	White Cells	Platelets	Differential					Comment
					Lymphocytes	Polymorphonuclears	Monocytes	Eosinophils	Basophils	
9/ 1/31	5.22	96	17,400	.....	23	77	0	0	0	
9/24/31	5.00	74	29,000	100,000	78	20	0	0	0	Coagulation time, 2.5 min.; bleeding time, 15 min.
9/25/31	3.41	..	34,000	.....	70	21	7.5	2.5	0	Fragility test: from 0.44 to 0.32
9/28/31	2.46	65	38,100	.....	77	16	2.5	1.5	1	
10/ 1/31	....	42	38,700	10,000	82	11	5	1	0	
10/ 3/31	2.42	45	44,900	.....	87	16	0	1	0	
10/ 9/31	1.90	..	18,300	40,000	82	18	0	0	0	
10/13/31	2.31	46	18,000	.....	81	14	0	1	0	

from 1 to 2 cm. in diameter, which were firm and tender to palpation, were scattered over the body. Small hemorrhages were present in the mucous membranes of the nose and mouth. The tonsils were swollen, edematous and necrotic. The cervical lymph nodes were enlarged, some of them being bean-sized and boggy, and others pea-sized and firm. The axillary, epitrochlear and inguinal glands were also the size of a small bean. No mass was found in the chest, and the lungs were clear. The heart was not displaced. The liver was not palpable. The spleen extended two fingerbreadths below the costal margin. Roentgen examination made at this time showed no increase in the mediastinal shadow, and the long bones were normal. The blood picture strongly suggested a leukemic process (table 5).

In view of the clinical history and physical findings, it was felt at this time that a diagnosis of a tumor of lymphatic origin, probably of the nature of a leukosarcoma, with a leukemic blood picture, could be made. It was thought probable that the roentgen therapy might have hastened the progress of the condition.

The subsequent course was typical of that of acute leukemia. The child had a temperature of from 101 to 101.4 F. and almost constant hemorrhages from the nose and throat, and he grew rapidly weaker. The superficial lymph nodes, especially those in the cervical region, increased to the size of a hazelnut. The spleen did not enlarge further, however. The blood picture was that of progressive anemia with a lymphocytosis. Mitotic figures in the blast forms were seen, and

immature forms of granulocytes were also present. Before death the number of normoblasts increased decidedly. On the morning of October 13, there was profuse bleeding from the left tonsillar region. The patient became comatose and died. A permit for autopsy could not be obtained.

(This case is presented through the courtesy of Dr. Joseph Brennemann and Dr. Milo Pierce.)

COMMENT

The cases herein presented demonstrate that lymphosarcoma is a precursor of lymphatic leukemia. The peculiarity of these cases lies in the apparent effect of deep roentgen therapy on the development of the acute leukemic state and the final condition of the tissues at autopsy. It has been repeatedly shown by numerous investigators that the roentgen rays have an elective influence on the immature nuclei of rapidly multiplying cells. While this is clearly seen in these cases, as manifested by clinical improvement of the patients, there are evidences of other seriously deleterious effects on the hematopoietic and other vital organs. Some authors even think that this method of treatment accelerates the final outcome. In the cases presented at autopsy the bone marrow was found to be fatty, and the direct smears made from this marrow were quite cell-poor, indicating a state of aplasia. The kidneys showed interstitial infiltration with a mass of cells apparently with pyknotic and fragmenting nuclei, not associated with bacterial emboli. The very fact that the tissues of the various organs did not show typical lymphocytic infiltration may be explained on the basis of the far-reaching effect of deep roentgen therapy. The presence of numerous healing tubercles in some of the organs appears to be a mere coincidence. The bacterial emboli found in the lymph nodes are interpreted to be a secondary phenomenon due to granulocytopenia. Observations such as these compel us to raise a serious question as to the employment of roentgen rays in the treatment of this type of lymphosarcoma and leukemia.

Another important point in the proper evaluation of the condition studied is the sequence of events which in these patients led to terminal leukemia. The evidences seem to favor the belief that the lymphoblasts are first developed in a group of organs normally concerned in lymphopoiesis. Under certain stimuli, this process of lymphocytic differentiation is greatly accelerated, producing a pathologic hyperplasia of these organs. When the process is confined to the organs of primary involvement, the condition is lymphosarcoma or lymphoblastoma. When it extends to other organs belonging to the same system, by way of the lymphatics, it is designated as a metastasis. When this extension gets into the blood stream, it becomes leukemia. When the extension takes place into other organs not normally concerned with lymphopoiesis, such as the kidneys or the muscles, it is spoken of as a leukemic infiltration.

When both the organs and the blood show atypical proliferation, it is called by Sternberg leukosarcoma and by Pappenheim sarcoleukemia. After the organs are infiltrated by the lymphoblasts, the pathologic cells, possessed of abnormal power of multiplication, may cause a cellular hyperplasia, or the mere presence of the abnormal cells in these organs may set up a state of mesenchymal reaction, causing the undifferentiated cells of the mesenchyme to develop into lymphoblasts. In either event, the phenomenon is a true lymphoid metaplasia, or extralymphatic lymphopoiesis, analogous to the myeloid metaplasia often found in chronic myelogenous leukemia and in certain experimental conditions.

SUMMARY AND CONCLUSIONS

1. Two cases are reported in which the patients when first seen had lymphosarcoma with a normal blood picture; a short time later acute lymphatic leukemia developed, with a rapidly fatal termination. This is additional evidence in favor of the view that lymphosarcoma and lymphatic leukemia are only different stages in the same pathologic process.

2. Roentgen therapy was instituted in both of these cases immediately after a diagnosis of lymphosarcoma was made, and the question therefore arises as to whether or not this treatment induced the leukemic state.

TOXICITY OF PURIFIED BILE PREPARATIONS

III. INFLUENCE ON CARDIOVASCULAR RESPONSES

FRED A. RIES, M.D.
AND
EUGENE U. STILL, PH.D.
BALTIMORE

In a previous paper [1] we reported on the toxic effects of purified bile salts on the neuromuscular system. We found the neuromuscular junctions and reflex centers of the cord to be affected by small quantities of bile salts, whereas the skeletal muscle was relatively unaffected by similar amounts of the salts. We have investigated other nerve end-organs or junctions and reflex centers.

In 1905 Meltzer and Salant [2] first showed that the intravenous injection of bile increased the response to peripheral stimulation of the vagus in anesthetized rabbits. In some of their experiments stimuli which were subminimal became effective after the intravenous injection of bile. They did not determine the quantity of bile acids contained in the bile. However, the content was sufficient to cause a marked fall in the blood pressure. King and Stewart [3] suggested that the bradycardia frequently seen in chronic jaundice is due to the bile pigment. These workers claimed to have worked with bile pigment (bilirubin) in their experiments. However, since they gave no evidence of the purity of their preparation, we believe that it was contaminated with the toxic bile acids. This view is held since recent works proving the nontoxic nature of bilirubin have been published by Horrall,[4] Horrall and Carlson [5] and Still.[6] Buchbinder and Kern [7] reported experiments indicating that the threshold of nervous excitability is elevated in obstructive jaundice. Buchbinder [8] suggested that the bradycardia observed by him

From the departments of physiology, the University of Chicago and the University of Maryland Medical School.

1. Ries, F. A., and Still, E. U.: Am. J. Physiol. **91**:609, 1930.
2. Meltzer, S. J., and Salant, W.: J. Exper. Med. **7**:1, 1905.
3. King, J., and Stewart, H. A.: J. Exper. Med. **11**:673, 1909.
4. Horrall, O. H.: J. Lab. & Clin. Med. **14**:1, 1928.
5. Horrall, O. H., and Carlson, A. J.: Am. J. Physiol. **85**:591, 1928.
6. Still, E. U.: Am. J. Physiol. **88**:729, 1929.
7. Buchbinder, W. C., and Kern, R.: Experimental Obstructive Jaundice: II. Modification of the Parathyroid Tetany Mechanism in Jaundice, Arch. Int. Med. **41**:754 (May) 1928.
8. Buchbinder, W. C.: Experimental Obstructive Jaundice: III. Age Factor in the Production of Bradycardia, Arch. Int. Med. **42**:743 (Nov.) 1928.

in jaundiced puppies (ligation of the common duct) was a specific reflex through the vagi.

Most workers now agree that the toxicity of bile resides in the bile salts. However, recently Thomas[9] concluded that neither glycocholate nor taurocholate affects the cardial rhythm, and that therefore neither could cause the bradycardia seen in jaundice.

Although some clinical investigators deny the co-existence of obstructive jaundice and bradycardia, others have observed that they are frequently associated. This work was undertaken in order to investigate the effect of purified bile salts on cardiovascular responses to nerve stimulation and some vasomotor reflexes. In these experiments we have used purified sodium cholate (Still[8]) and sodium dehydrocholate. Sodium dehydrocholate, which is of relatively low toxicity, was employed because the induction of changes in irritability was produced more gradually than with sodium cholate, and therefore the various stages could be followed with greater ease. The experiments were carried out on dogs, cats and rabbits under anesthesia produced by sodium barbital (275 mg per kilogram) or chloralose (8 mg. per kilogram).

In most of the experiments the vagi were sectioned in the neck to exclude reflex cardiac inhibition. Mixed pressor-depressor responses were obtained by stimulation of the central end of the vagus nerve and the sciatic nerve. Cardiac inhibition was elicited by peripheral stimulation of the vagus nerve. In rabbits (with vagi intact) the same response was obtained by stimulation of the central end of the depressor nerve. The duration and intensity of the stimulating current were kept constant. Reflex pressor responses were elicited also by temporary occlusion of the carotid arteries. The responses of the sympathetic division of the autonomic system were studied by the injection of epinephrine hydrochloride solution.

STIMULATION OF NERVES

Vagus Nerve: Peripheral End.—Figure 1 shows the effect of intravenous injection of a small dose of the relatively nontoxic sodium dehydrocholate. It will be noted that stimulation of the peripheral end of the vagus nerve caused a greater and more prompt (shorter latent period) decrease in the blood pressure after the injection than in the control. If a larger amount of sodium dehydrocholate is injected in broken doses (total of 150 mg. per kilogram) this period of hyperirritability is followed by progressive decrease in response and finally by the development of a block. The block is a relative one, for increase

9. Thomas, E.: Rev. méd. de la Suisse Rom. **50**:207, 1930.

in the intensity of the stimulus produces a decrease in blood pressure comparable to that in the control.

The intravenous injection of smaller doses of the more toxic sodium cholate (25 mg. per kilogram) causes a shorter period of hyperirritability and a more rapid onset of depression and block. In most of our observations the decreased excitability affected the left vagus to a greater degree than the right one. If the sodium cholate is injected in small broken doses (total of 22 mg. per kilogram), hyperirritability

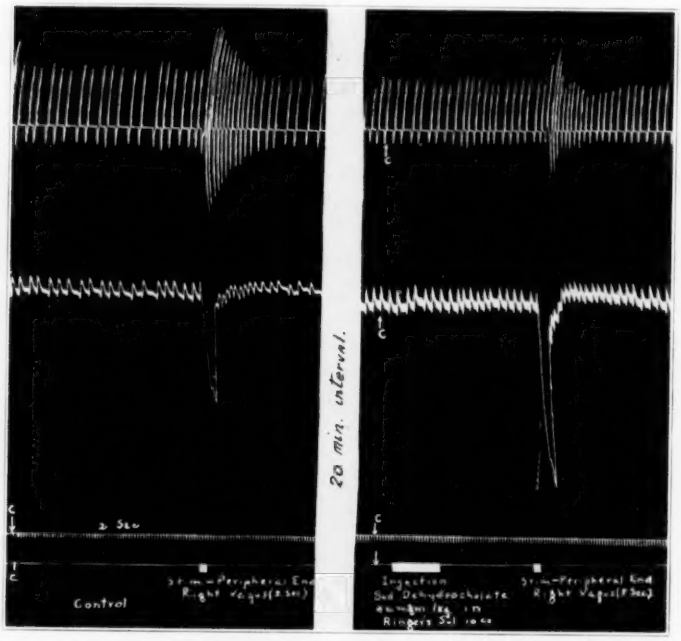


Fig. 1.—Tracings on a dog (barbital anesthesia; both vagi sectioned). Effect of peripheral stimulation of the vagus nerve before and after the injection of 40 mg. of sodium dehydrocholate per kilogram intravenously.

only may be encountered and may persist for an hour or longer after the first injection.

It seems probable that the main influence is on the myoneural junction in the heart, because of the following facts: 1. The local application of higher concentrations of bile salt than those used in these experiments apparently does not alter the conduction through the fibers of the vagus nerve. This is shown by the normal action currents and by the normal response of the heart to a stimulus applied at a point distal to a point on the vagus trunk where the bile salt was applied. 2. Stimu-

lation of the central end of the vagus nerve produces marked reflex changes in blood pressure at a time when peripheral stimulation shows depression of irritability or block.

Vagus Nerve: Central End.—Figure 2 shows the effect of stimulation of the central end of the right vagus nerve following the intravenous injection of a small dose of sodium cholate (17 mg. per kilogram). It will be noted that three minutes after the injection stimulation caused a more prompt (shorter latent period) and a more marked pressor response than in the control, but after an interval of ten minutes there were a prolongation of the latent period and a marked decrease in the extent of the pressor phase with an increase in the depressor portion of the reflex. As shown in figure 3, following the

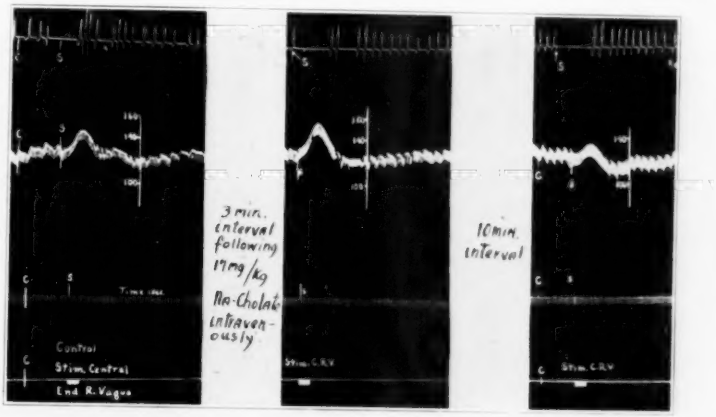


Fig. 2.—Tracings on a dog (barbital anesthesia; both vagi sectioned). Effect of central stimulation of the vagus nerve before and after the injection of 17 mg. of sodium cholate per kilogram intravenously.

subsequent injection of sodium cholate (total of 37 mg. per kilogram) there was absence of the pressor phase with only a depressor response. The vasomotor center was able to respond to anemia caused by increasing the intracranial pressure (introduction of warm saline solution under pressure).

In dogs in which a depressor response only was elicited on control stimulation of the central end of the vagus nerve, the injection of sodium dehydrocholate (40 mg. per kilogram) caused this reflex decrease in blood pressure to become more marked and the duration of the latent period to be shortened.

We have recognized the fact that frequently one may obtain either pressor or depressor responses from central stimulation of the vagus, and that the predominating response may alternate from one to the

other. However, in all of our experiments by this particular plan (ten) the response in every case was predominately depressor after the injection of bile salts, and in most of the cases the pressor phase was entirely absent.

Depressor Nerve.—Following the administration of a small dose of sodium cholate or sodium dehydrocholate in rabbits there first appears a diminished response of the blood pressure to stimulation of the central

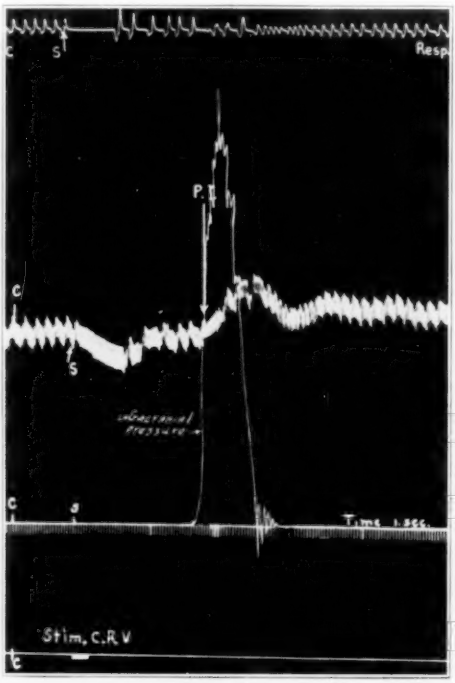


Fig. 3.—Tracings on the same dog as in figure 2 after a total of 37 mg. of sodium cholate per kilogram had been injected intravenously in broken doses. For control see figure 2. On stimulation of the central end of the cut vagus nerve only the depressor phase was elicited. Raising of the intracranial pressure produced, however, a pressor response.

end of the depressor nerve. This is later followed by a period during which an augmented depressor effect may be obtained. We did not obtain a reversal of this reflex, as is frequently seen following the injection of ergotamine.

Sciatic Nerve.—Following the intravenous injection of sodium dehydrocholate (50 mg. per kilogram) the pressor effect on stimulation

of the central end of the sciatic nerve becomes more marked and may remain so for several hours. Figure 4 shows this increase in irritability. If one injects the more toxic sodium cholate (from 25 to 30 mg. per kilogram), this period of hyperirritability is present but is soon followed by a decreased pressor response and then block. This is a relative block as a stronger stimulus will cause a response (as we found in the peripheral vagus experiments). We interpret this as indicating an increased threshold of the sympathetic synapses or endings.

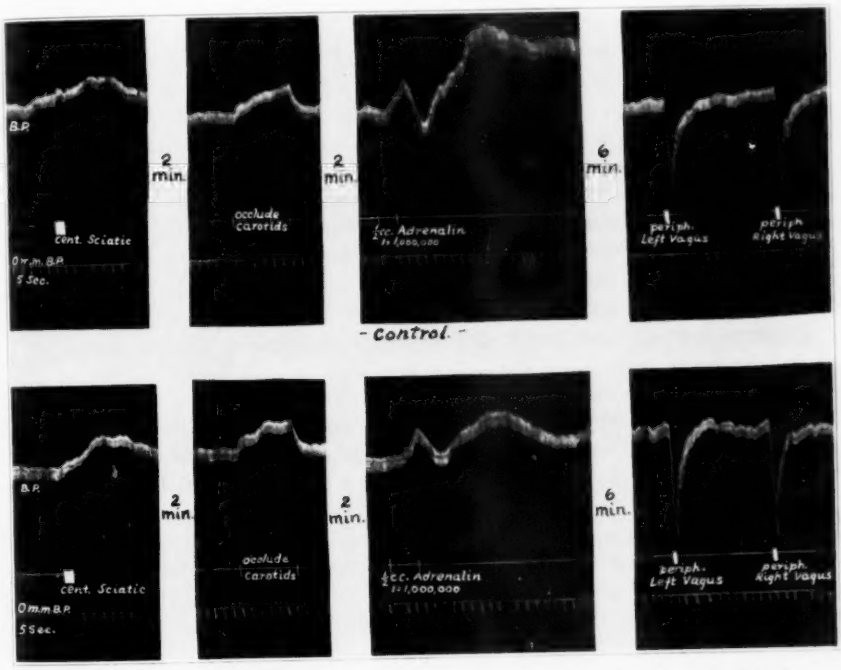


Fig. 4.—Tracings on a cat (chloralose anesthesia; both vagi sectioned). Blood pressure from femoral artery. Above: control on the effect of stimulation of the sciatic nerve, occlusion of carotid arteries, intravenous injection of epinephrine and stimulation of the peripheral ends of the cut vagus nerves. Below: control after the intravenous injection of 50 mg. of sodium dehydrocholate per kilogram.

OCCLUSION OF THE CAROTID ARTERIES

The carotid reflex was elicited by temporary occlusion of the common carotid arteries. Figure 4 shows the effect on this response of the intravenous injection of 50 mg. of sodium dehydrocholate per kilogram. Following the injection of the bile salt the reflex increase in blood pressure became slightly more marked than in the control. This hyper-

irritability persisted, though to a less marked degree, for two and one half hours after the injection. The intravenous injection of smaller doses of the more toxic sodium cholate (20 mg. per kilogram) is followed by this persisting hyperirritable pressor reflex. In five of six experiments the pressor effect of occlusion of the carotids was more marked following the injection of bile salts than in the control; in the remaining experiment there was a primary period of decreased response followed by a pressor action greater than in the control. Large doses of bile salts were required to depress this reflex.

INJECTION OF EPINEPHRINE HYDROCHLORIDE

Luckhardt and Koppanyi [10] showed that when epinephrine is administered repeatedly at too short intervals there is a progressive decrease in its effects. Our epinephrine hydrochloride solutions were prepared just before use and kept in a chilled, stoppered container. The interval between the injections was at least fourteen minutes. We found in control experiments in which no bile salt was administered that the frequency and number of injections of epinephrine used by us did not fatigue the pressor mechanism.

Figure 4 shows the decrease in the response to intravenously administered epinephrine (0.5 cc. of a 1:1,000,000 solution) after the intravenous injection of 50 mg. of sodium dehydrocholate per kilogram. The duration, as well as the magnitude of the response, was decreased at a time when the vagal endings were shown to be hyperirritable. The pressor effect of epinephrine was still diminished two and a half hours after the injection of the bile salt. Similar results are obtained if one injects a small dose of the more toxic sodium cholate (from 20 to 25 mg. per kilogram). In those experiments in which epinephrine gave primary and secondary pressor responses after the control injection, following the administration of bile salts in relatively large amounts, the same dose of epinephrine gave but one rise of decreased magnitude and duration. As a matter of fact, in all of our experiments doses of less than 100 mg. of sodium cholate per kilogram obliterated the pressor response to epinephrine.

We did not observe a primary increase in irritability of the sympathetics as we did in the vagus and neuromuscular systems.

EFFECT OF INCREASED INTRACRANIAL PRESSURE

In order to determine the irritability of the central vasomotor mechanism after the injection of bile salts we produced anemia of the center

10. Koppanyi, T., and Luckhardt, A. B.: Arch. internat. de pharmacodyn. et de thérapie **40**:344, 1931. Luckhardt, A. B., and Koppanyi, T.: Am. J. Physiol. **81**:436, 1927.

by increasing the intracranial pressure (introduction of physiologic solution of sodium chloride under pressure into the cavity). The increased intracranial pressure was accompanied by a compensatory increase in blood pressure. Figure 3 shows the effect at a time when only depressor responses were obtained by stimulation of the central end of the vagus nerve. Moreover, asphyxia (clamping of the trachea) caused a marked pressor effect at a time when the pressor action of epinephrine hydrochloride or reflex pressor responses were greatly decreased or absent.

COMMENT

Jenke and Steinberg [11] have reported that normal human blood contains 0.025 mg. of bile salts per hundred cubic centimeters, while blood from icteric patients contains from 2 to 8 mg. In our experiments we have injected from 10 to 40 mg. of the salts per kilogram of body weight (in a few cases we have injected as much as 100 mg. per kilogram). Assuming the circulating blood to be about 8 per cent of the body weight, we have caused an initial concentration of bile salts of from one to four times that found by Jenke and Steinberg in icteric patients. Within a few minutes, however, the concentration would be reduced by dilution with the other body fluids to approximately 50 per cent of the initial concentration. Our initial concentrations of blood are especially comparable to those found by Jenke and Steinberg when one considers our experiments with the less toxic salt, sodium dehydrocholate.

Our experiments suggest that following the entrance into the circulation of small amounts of bile salts, there is a hyperexcitability of the vagus endings or junctions and depression of the vasoconstrictor endings. This removal of the antagonistic influence of the sympathetic endings would permit vagal predominance and may account for the bradycardia noted by Buchbinder [6] during the early stages of obstructive jaundice in puppies. We believe that the diminished response to epinephrine was due mainly to depression of the vasoconstrictor endings or junctions. In three experiments in which the vagi were cut, the change in amplitude and rate of the pulse following the intravenous injection of epinephrine was about the same before and after the injection of the bile salts. If the bile salts affected mainly the cardiac muscle, as is supposed by Buchbinder, one would expect the cardiac response to epinephrine to be different in the two cases.

The later progressive decrease in vagus irritability and the introduction of a relative block at the vagal endings or junctions due to the toxic action of bile salts suggest an explanation for the periods of relative and absolute tachycardia noted by Buchbinder in the puppies

11. Jenke and Steinberg: Arch. f. exper. Path. u. Pharmakol. **153**:244, 1930. Jenke: ibid. **163**:175, 1931.

following the primary bradycardia. The possibility remains, however, that the lower blood calcium (Andrews, Rewbridge and Hrdina,[12] and Buchbinder and Kern[13]) may play a rôle in the production of tachycardia late in obstructive jaundice. The tachycardia may be of other than sinus origin. It is interesting to note that Buchbinder and Kern reported variation in pulse rate in frogs following obstruction of the common duct. These phenomena would partially account for the hypotension noted in obstructive jaundice, other factors being myocardial involvement, gastro-intestinal disturbance and malnutrition. The tendency toward hypotension may be partly counteracted by a reflex involving the carotid sinus, as indicated from our experiments, for rather large amounts of bile salts are required to depress this reflex.

In the experiments with intact vagi we have not detected significant changes in the pulse following the injection of bile salts because of the diminution or absence of vagus tone in anesthetized animals.

It is our opinion that an important factor in the development of bradycardia observed clinically is the increased sensitivity of the vagus endings (or junctions) and the decreased sensitivity of the sympathetic endings (or junctions). This opinion is further supported by the recent work of Jenke and Steinberg on the concentration of bile salts in normal and icteric men.

In the doses employed in these experiments only the large amounts of bile salts affected the toxic discharge of the vasomotor center. Small amounts of bile salts at first decrease the latent period and increase the extent of the reflex pressor responses. Larger amounts of bile salts (or a more toxic salt) prolong the latent period and alter the extent of the vascular reflexes at a time when the vasomotor mechanism can react readily to anemia. This suggests that the alteration occurs in the region of the efferent side of the center.

CONCLUSIONS

These experiments seem to warrant the following conclusions as to the site of action and the effect of purified bile salts on cardiovascular response:

1. Bile salts do not materially affect conduction through nerve fibers.

2. Small concentrations of bile salts increase the irritability of the vagal endings or junctions, and the same amounts decrease the sensitivity of the vasoconstrictor endings or junctions.

12. Andrews, E.; Rewbridge, A. G., and Hrdina, L. S.: Proc. Soc. Exper. Biol. & Med. **27**:755, 1930.

13. Buchbinder, W. C., and Kern, R.: Am. J. Physiol. **80**:273, 1927.

3. The injection of large doses of bile salts tends to produce block (relative or absolute) of the endings of both systems.

4. These factors are probably involved in the production of the changes in the pulse rate noted in obstructive jaundice.

5. The medullary centers are more resistant to bile salts than are their peripheral components.

SPLENECTOMY IN SICKLE CELL ANEMIA

REPORT OF A CASE WITH NECROPSY IN AN ADULT ON WHOM SPLENECTOMY WAS ATTEMPTED

R. E. CHING, M.D.
AND
L. W. DIGGS, M.D.
MEMPHIS, TENN.

The physician faced with the care of a patient with severe sickle cell anemia, with its characteristic hemolytic jaundice, recurrent attacks of pains in the muscles and joints, abdominal symptoms, ulcers of the legs, fever and increased susceptibility to intercurrent infections, is likely, after the usual antianemic measures have failed, to give serious consideration to any procedure which offers hope of benefit. Splenectomy,[1] first suggested by Sydenstricker on the basis of the similarity of the disease to congenital hemolytic icterus, has been given a prominent place in the literature as a means of treatment. The results of the removal of the spleen have been reported in seven instances.[2] All the splenectomies have been performed on children. The trend of opinion in regard to the procedure is optimistic, and one is likely to be impressed by the enthusiastic claims for surgical cure. The negative or unfavorable results and contraindications are not so obvious unless a critical analysis of the recorded data is made.

It was our unfortunate experience to have advised splenectomy on a young adult with active sickle cell anemia. At operation no spleen

From the Department of Pathology, Pathological Institute, University of Tennessee.

1. Sydenstricker, V. P.: Sickle Cell Anemia, South. M. J. **17**:177 (March) 1924.

2. (*a*) Hahn, E. V., and Gillespie, E. B.: Sickle Cell Anemia. Report of a Case Greatly Improved by Splenectomy. Experimental Study of Sickle Cell Formation, Arch. Int. Med. **39**:233 (Feb.) 1927. (*b*) Stewart, W. B.: Sickle Cell Anemia. Report of a Case with Splenectomy, Am. J. Dis. Child. **34**:72 (July) 1927. (*c*) Bell, A. J.; Kotte, R. H.; Mitchell, A. G.; Cooley, T. B., and Lee, Pearl: Sickle Cell Anemia. Report of Two Cases in Young Children in which Splenectomy was Performed, Am. J. Dis. Child. **34**:923 (Dec.) 1927. (*d*) Hahn, E. V.: Sickle-Cell (Drepanocytic) Anemia, with Report of a Second Case Successfully Treated by Splenectomy and Further Observations on the Mechanism of Sickle-Cell Formation, Am. J. M. Sc. **175**:206 (Feb.) 1928. (*e*) Landon, J. F., and Lyman, A. V.: Sickle Cell Anemia with Case Report of Splenectomy, Am. J. M. Sc. **178**:223 (Aug.) 1929. (*f*) Leivy, F. E., and Schnabel, T. G.: Abdominal Crises in Sickle Cell Anemia, Am. J. M. Sc. **183**:381 (March) 1932.

was found, and the patient died. In order that others may avoid our mistake, the case is reported. Evidence for or against splenectomy is weighed, and the essential pathology of the disease is emphasized. Further justification of this paper lies in the fact that extensive clinical and hematologic studies were made over a two year period, and a complete autopsy was performed.

REPORT OF A CASE

History.—A. L. C., aged 18 years, an unmarried Negress from Mississippi, was observed at frequent intervals in the outpatient department of the Memphis General Hospital, and on four occasions was admitted to the wards. The early history is fragmentary, as the patient was illegitimately born and from early infancy lived with relatives. Nothing is known concerning the health of the father, but the mother worked regularly, had no history of anemia and did not possess the sickle cell trait.

At school and while working in the cotton fields, the patient tired more easily than other children and took little part in their play. The diseases of childhood were not followed by complications, and there were no serious illnesses. Sore throats, colds, digestive disturbances and pains in the joints were frequent. During childhood she often had "cat boils," a chronic type of ulceration which heals slowly, and which is said to be common among Negroes on plantations. At the age of 14, a large ulcer appeared on the anterior of the right leg, just above the ankle, which did not heal for a year.

When 16 years of age, the patient obtained employment as a nurse maid, but found the work heavy and was unable to keep a position because of attacks of sickness in which symptoms in the joints and abdomen were prominent.

Examination.—In March, 1928, at the age of 18, she reported to the outpatient department with the complaint of menorrhagia associated with fever, epistaxis, abdominal pain and leukorrhea. Physical examination revealed a tall, slender girl, of average intelligence, appearing younger than her given age, with a prominent forehead, scanty pubic and axillary hair and poorly developed external genitalia. Other findings of importance were jaundice, pallor, tonsillar hypertrophy, general enlargement of the lymph glands, a nontransmitted systolic murmur, low blood pressure, hepatomegaly, infantile uterus, edema of the ankles and round, depressed scars of numerous ulcers on the shins of both legs. The lungs were clear, and the spleen not palpable. Cervical smears were negative for gonococci. The Wassermann reaction was 4 plus. The gallbladder was not visualized by the Graham test. Intramuscular treatment with mercury salicylate was instituted. There was no improvement.

In May, 1928, she was admitted to the gynecologic ward with the diagnosis of an acute condition of the abdomen, the symptoms of which were severe pain in the lower part of the abdomen, nausea and vomiting. The temperature was 103 F., and there was marked abdominal tenderness. The leukocyte count was 28,000; the erythrocyte count, 2,800,000, and the hemoglobin, 20 per cent (Sahli). There was definite jaundice, with an icteric index of 42. A flat plate failed to reveal gallstones. Cultures of the blood and stool gave negative results. The acute symptoms subsided within a few days, and the general condition gradually improved. She was discharged at the end of two months, with the diagnosis of "acute salpingitis, syphilis and cholecystitis with jaundice." Sickle cell anemia was not suspected.

During the next year she "just ailed around" and became extremely weak. An unproductive cough developed, and she began to have night sweats. She lost 55 pounds (24.9 Kg.). The menses became irregular and scanty, and were often accompanied by pain in the lower quadrant and epistaxis. Episodes of severe pains in the muscles and joints were frequent. Nocturia developed.

In April, 1929, an injection of mercuric salicylate was followed by stomatitis and an exaggeration of the abdominal symptoms. She was admitted to the medical service and remained under observation for two months. The physical findings were unchanged.

An examination of the blood which was made on this admission revealed a severe hemolytic anemia with evidence of active regeneration. The values for the red

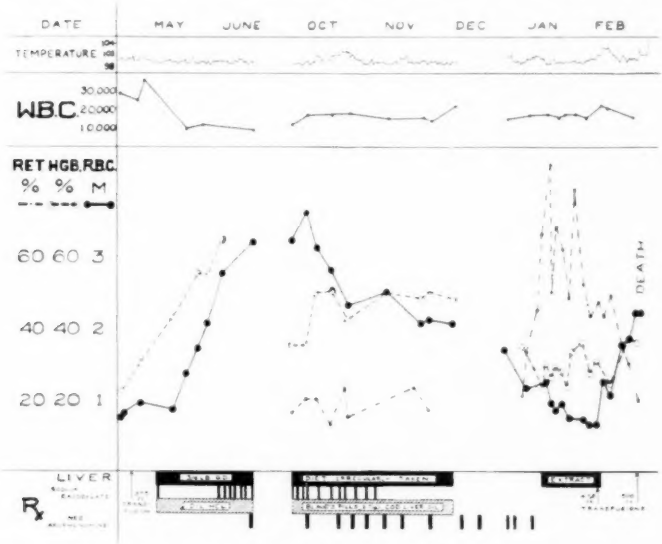


Fig. 1.—Chart showing temperature and the values in leukocytes, erythrocytes, hemoglobin and reticulocytes in relation to therapy.

and white blood cell counts, hemoglobin and reticulocytes for this and subsequent admissions are given in figure 1. The color index was variable. The volume of packed red blood cells was 23 cc. per hundred cubic centimeters of whole blood. The mean corpuscular volume was 73 cubic microns; the mean corpuscular hemoglobin, 27 micromicrograms, and the mean corpuscular hemoglobin concentration, 37 per cent. When a drop of blood was sealed under a coverslip and examined immediately, only occasional pointed erythrocytes were noted. On standing, the bizarre and spiked red cells rapidly appeared, reaching a maximum of from 80 to 100 per cent in from eighteen to thirty hours. The erythrocytes readily became sickle cells in brilliant cresyl blue preparations, and it was noted that the mature cells without reticulum showed a higher percentage of sickle cells than did the heavily reticulated cells (fig. 2). The pointed rod and slender crescent forms so numerous and typical in the stained smears in some cases of sickle cell anemia in this case were difficult to find. Constant features of the dry smear preparations were anisocytosis, aniso-

chromia, moderate poikilocytosis, diffuse basophilia, Jolly's bodies, megaloblasts, nucleated red blood cells and numerous platelets. Mitotic megaloblasts, stippled cells and phagocytosis of erythrocytes by large mononuclear cells were observed, but were infrequent.

Leukocytosis was constant. The differential formula showed an increase in the immature granulocytes, and a normal percentage of polymorphonuclears with four and five lobes. The eosinophils were not increased on the first two admissions, but later averaged 10 per cent. The average mononuclear percentage was 3.

The platelets were consistently increased, and were often large and well preserved. The bleeding time was seven minutes. The coagulation time (capillary pipet method) was one and one-half minutes. The clot was firm and retracted well. The fragility test revealed beginning hemolysis at 0.36 per cent of sodium chloride, and complete hemolysis at 0.24 per cent of sodium chloride.

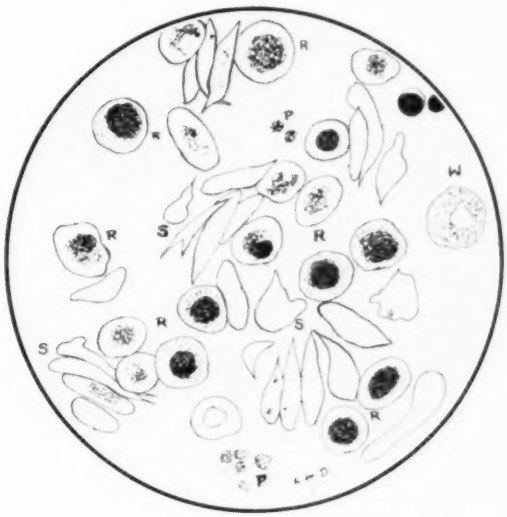


Fig. 2.—Moist, brilliant cresyl-blue preparation. Drawing of an actual oil immersion field, showing numerous reticulated erythrocytes, most of which are nucleated. The nonreticulated cells sickle to a greater degree than those containing a great amount of dye. *R*, reticulated red blood cells; *S*, sickled red blood cells; *W*, degenerated leukocyte, and *P*, platelets.

The urine showed urobilin, traces of albumin, occasional hyaline and finely granular casts, and a few red blood cells. The phenolsulphonphthalein test yielded a 35 per cent excretion in the first hour and a 25 per cent excretion in the second. The nonprotein nitrogen was from 24 to 30 mg. per hundred cubic centimeters of blood, and the creatinine, 1.4 mg. No free hydrochloric acid was found in the gastric contents before or after the test meal. Blood cultures were negative. A roentgenogram of the chest showed slight left ventricular hypertrophy.

Treatment.—Following a transfusion of 375 cc. of whole blood the patient was placed on a diet of liver, and in addition given sodium cacodylate, dilute hydrochloric acid, and mercury and iodide tablets. The clinical condition slowly

improved. There was a steady increase in the erythrocytes and hemoglobin, and a decrease in leukocytes (fig. 1). During this stay in the hospital there were low grade intermittent fever and occasional attacks of abdominal pain. The patient was discharged in July, 1929.

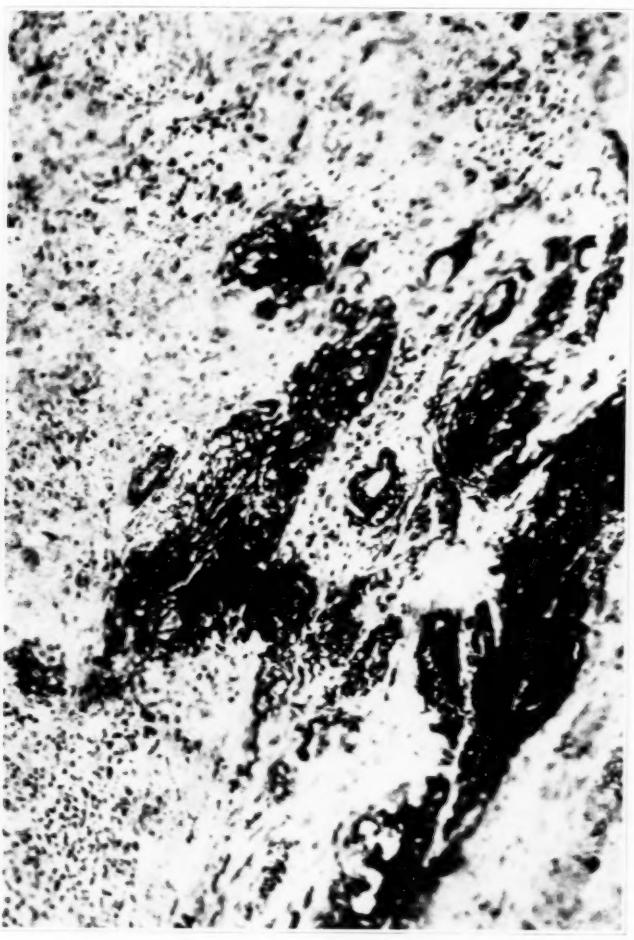


Fig. 3.—Spleen; increased amount of connective tissue containing black staining, calcareous material. Reduced from a magnification of × 200.

During the remainder of the summer the patient was unable to continue on a regular diet of liver, her varied symptoms continued, and in September of the same year she was again admitted. The findings were essentially the same as on previous admissions. The red cell count was 3,200,000, and the hemoglobin, 35

per cent (Sahli). Jaundice persisted; the icteric indexes varied from 25 to 50. The stools were dark brown, and there was urobilinuria. Gastric analysis again revealed an absence of free hydrochloric acid. The temperature remained elevated, and sweating was profuse. Abdominal pains, distress after eating and nausea were often complained of. Epistaxis occurred on two occasions. Headaches were frequent. There were three attacks of severe pain in the joints and backache, lasting from two to five days. Partial relief was obtained by the use of salicylates and hot applications. The attacks disappeared without leaving residual soreness or limitation of movement. In one attack there were severe pain and stiffness of the

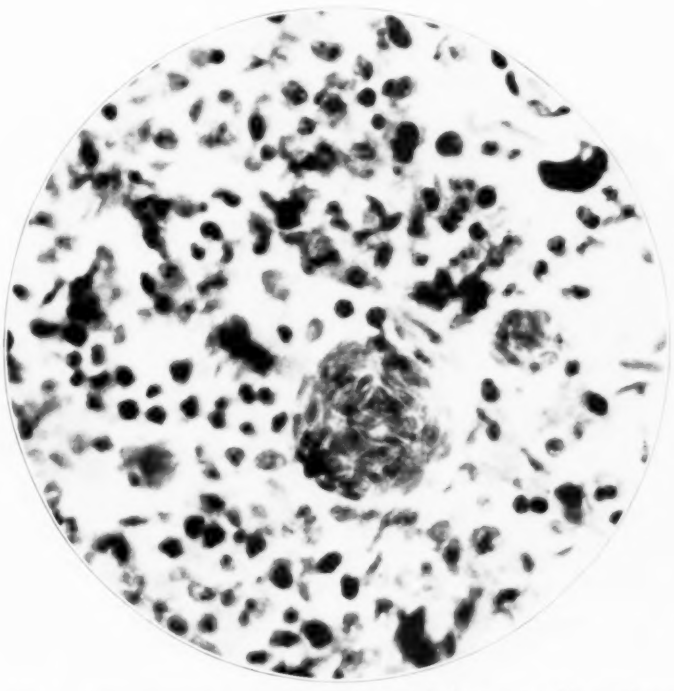


Fig. 4.—Bone marrow; general hyperplasia and clumps of sickle erythrocytes resembling agglutinated corpuscles. Magnification, × 750.

left arm, and the wrist was definitely swollen and hot. At another time the patient complained of pain in both wrists, and later of backache and immobility of the left thigh. The therapy and progress of the anemia are shown in figure 1. A striking change in the blood picture at this time was the development of marked eosinophilia and a diminution in the number of nucleated red blood cells. The general condition remained unaltered, but the patient was allowed to go home.

Seventeen days after discharge she was back in the hospital, with the complaint of stiffness in the right arm and left leg, severe pain in the left upper quadrant and "shaking chills." The left ankle and right wrist were swollen, with a local

increase in temperature. There was a profuse vaginal discharge. The symptoms and signs of anemia were more severe, the systolic murmur more pronounced and the liver larger.

On this admission the blood picture was that of a most striking regeneration, with numerous premature cells of the erythrocytic and myeloid series present. On Jan. 14, 1930, the percentage of reticulocytes reached 87, and nucleated red blood cells outnumbered the leukocytes. Following the administration of liver extract, 3 ampules a day, the reticulocytes decreased somewhat, but the erythrocytes continued to fall, and the hemoglobin did not significantly change. Peculiarly, the icteric index figures were lower than on previous admissions, being 9 and 19.

In view of the tendency of the anemia and clinical symptoms to become progressively worse, in spite of intensive therapeutic measures, splenectomy was con-

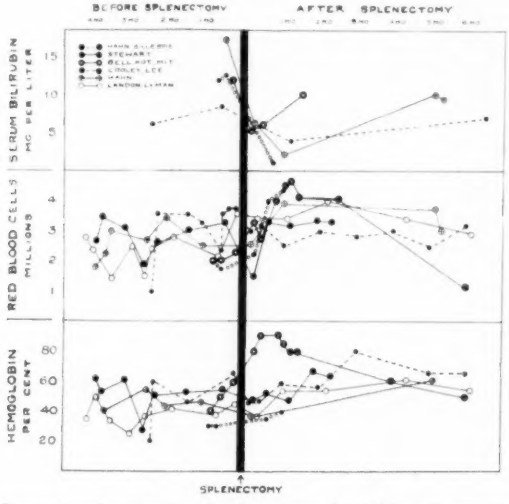


Fig. 5.—Chart showing results of splenectomy in sickle cell anemia. Preoperative and postoperative values in serum bilirubin, red cells and hemoglobin in six reported splenectomies.

sidered the only remaining hope. A preoperative transfusion was given, but a tonsillar abscess developed, and the operation was withheld until it subsided. Another transfusion was given, and an exploratory laparotomy was done by Dr. McGehee through a left rectus incision. The spleen could not be found. Following the operation, the patient's condition became critical, and death occurred on the next day.

Autopsy.—Gross Findings: Autopsy was performed within an hour after death. All tissues were deeply icteric. The serous cavities contained a slight excess of clear, yellow fluid. There were many adhesions about the gallbladder, in the region of the spleen and in both pleural cavities.

The heart weighed 250 Gm. and was devoid of gross abnormalities. The middle lobe of the right lung was studded with numerous tubercles. The bronchial glands were large and caseous.

The liver weighed 2,210 Gm.; it was of average consistency and rust brown. Each kidney weighed 200 Gm. and was of a color similar to that of the liver. The gallbladder was thin-walled and contained no stones. The bile ducts were patent.

What proved to be the spleen was a tiny, nodular unit lying flat against the diaphragm and deeply buried in dense adhesions. It weighed 10.5 Gm. and was very firm. The dark red pulp was partitioned into many small units by yellowish scars.

The retroverted uterus measured 5 by 2.5 by 2 cm. The tubes and ovaries were small. There were no pelvic adhesions.

There was general enlargement of the lymph glands, the largest measuring from 1 to 2 cm. in diameter. With the exception of the bronchial glands, all the glands were discrete, brown and soft.

The aorta was thin and elastic. The intima was smooth.

The skull was thickened, the greatest dimensions (2 cm.) being in the parietal regions. The inner surface of the shaft of the femur was irregular and penetrated in a few places by soft red marrow. The marrow of the femur, ribs and vertebrae was red and semifluid.

The other organs showed nothing noteworthy.

Bacteriologic studies of the heart's blood, bone marrow and spleen revealed no organisms on smear or culture.

Microscopic Findings: The studies of the tissues were made on material fixed in a solution of formaldehyde, embedded in celloidin and stained with hematoxylin-eosin.

In every tissue most of the erythrocytes were uniformly greatly elongated and fusiform.

Sections from the middle lobe of the right lung showed many miliary and conglomerate tubercles, especially around the larger bronchi and blood vessels. There was little caseation or encapsulation. The bronchial lymph glands showed large areas of caseation bordered by giant cells and epithelioid cells.

There was a small amount of perivascular infiltration of the round cells in the adventitia of the aorta, but no intimal or medial changes could be made out.

The blood capillaries of the liver were widely distended with sickle cells, which in many instances were clumped in large, round masses suggesting agglutination. The Kupffer cells were enormously increased in number and size, and frequently contained from three to six nuclei. They were laden with varying amounts of ingested sickle cells and pigment granules. As many as from 20 to 30 sickle cells were frequently seen within a single phagocyte. The polygonal cells exhibited a heavy deposit of amorphous brown pigment, concentrated more in certain areas, but lacking a zonal distribution. There was a heavy infiltration of the periportal spaces with small round cells, plasma cells, eosinophils and large mononuclears. A few epithelioid tubercles were found in every section.

The capsule, trabeculae and pulp of the spleen showed a great amount of scarring. Black-staining, slender, beaded threads parallel to the connective tissue fibers and concentrated in the vessel walls were a striking feature (fig. 3). After decalcification this material was no longer perceptible. In the capsule and the trabeculae were a few large, black and green staining granules, which on decalcification took a pink stain and resembled grains of starch. Some of these granules were within the cytoplasm of foreign body giant cells. In one of the trabeculae was a large, round, granular, red-staining body, with a thick capsule, resembling an Aspergillus head.

The pulp mostly consisted of extensive extravasations of sickle cells. The pulp cords were congested; the malphigian bodies were inconspicuous and fibrosed. Much of the pulp was extremely cellular, and showed numerous megalokaryocytes, plasma cells, small round cells, macrophages, polymorphonuclears and eosinophils. There were also a few islands of large, pale-staining, round cells (myelocytes?). No normoblasts could be recognized. All of the arteries and arterioles showed a thickened intima owing to proliferation of large, pale, vacuolated endothelial cells. Many of the lumens were obliterated. A few vessels showed breaks in their walls, which were infiltrated by round cells, plasma cells and fibroblasts.

The glomerular capillaries in the kidneys were engorged with sickle cells and capsular spaces filled with fat droplets and a granular, brown-staining material. Many convoluted tubules showed hyaline droplet degeneration. Everywhere the tubular epithelium contained numerous small, brown, amorphous, pigment granules, most marked in the convoluted portions. The collecting tubules contained hyaline, granular and fatty casts. There were a few small round cells in the interstices.

No fat could be found in the bone marrow. The marrow was rich in nucleated cells. Erythroblastic and leukoblastic islands were numerous. Polymorphonuclear neutrophils, eosinophils, pigment-laden macrophages and megalokaryocytes were present in large numbers. There were large clumps of small round cells resembling lymphocytes. Dispersed throughout the marrow there were numerous large, round cells, with pale, vesicular nuclei containing nucleoli, and having varying amounts of cytoplasm. With the Wright stain these cells were of an unclassifiable, primitive type. The sickle cells were as abundant in the reticular spaces as in the blood vessels. In many instances they were closely packed into large round masses, resembling the clumps found in the liver (fig. 4). There were a few large areas of hemoglobin which corresponded in size to the clumps of sickle cells.

The medulla of the lymph glands was distended with numerous large mononuclears, plasma cells, lymphocytes, pigment-laden macrophages and many other cells which could not be identified. No hemolymph glands were found.

In summary, the pathologic findings were jaundice, anemia, atrophy of the spleen with fibrosis and infiltration of calcium, hepatomegaly, hyperplasia of the bone marrow, thickening of the skull and irregularities in the cortex of the femur, general hyperplasia of the lymph glands and chronic mediastinal and terminal miliary tuberculosis.

COMMENT

The clinical, hematologic and autopsy observations reported in this case are characteristic of sickle cell anemia. Striking hematologic features are the extremely high counts for reticulocytes, the scarcity of sickle cells in the stained smears and the inconstant eosinophilia. No conclusions can be drawn as to the effect of liver or other therapy, because too many antianemic measures were concurrently employed, and the disease was complicated by syphilis and tuberculosis. Syphilis must be considered as a possible explanation of the indolent ulcers of the legs. In retrospect it is obvious that the continuation of neoarsphenamine in the presence of continued fever and progressive anemia was ill advised (fig. 1).

The symptoms and signs of sickle cell anemia are often suggestive of a pathologic condition which requires surgical intervention, and it is of interest that this patient was first admitted to the gynecologic service,

an acute condition of the abdomen being suspected. The clinical diagnosis of pelvic inflammatory disease was not confirmed by autopsy. On this first admission there was also an entire lack of appreciation of the factor of hemolysis in the production of the jaundice.

The inability of the surgeon to find the spleen at operation was readily explained at autopsy, for the fibrotic remnant was flattened out and so firmly adherent to the diaphragm that it appeared as part of it. The possibility of encountering a spleen too small to be removed should have been anticipated, because such is the characteristic finding in adult patients with sickle cell anemia. Sydenstricker [3] also attempted to perform splenectomy on an adult in whom the atrophic spleen was estimated to measure 6 by 4 cm. Bennett,[4] Jaffe,[5] Sydenstricker and others [6] and Steinberg [7] reported autopsies in which the spleen was as minute as in our case. That the spleen may undergo complete obliteration in active sickle cell anemia was shown in a recent autopsy on a man aged 51, in whom no remnant of splenic tissue could be found.

Splenomegaly has frequently been found in young children, and by many it is thought to be characteristic of the early stages of the disease. The essential feature of the pathologic condition of the spleen, according to Rich,[8] is congestion of the pulp, present in all in whom the sickle cells occur. In the active anemic state, this engorgement is extreme, and there may be hemorrhages and infarcts. Fibrosis follows, varying with the amount and duration of injury, and leads to shrinkage. Whether splenomegaly is always a characteristic early manifestation and whether fibrosis with atrophy always follows remains to be proved. Stewart [20] noted progressive enlargement of the spleen followed by atrophy in a child with successive anemic episodes. Much more data must be available before any definite conclusions can be drawn concerning the pathologic condition of the spleen in this disease.

SPLENECTOMY IN SICKLE CELL ANEMIA

Recorded opinion as to the value of splenectomy in sickle cell anemia is divided. Hahn [21] stated that profound anemia is an indication rather

3. Sydenstricker, V. P.: Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12 (July 5) 1924.

4. Bennett, G. A.: Sickle Cell Anemia. Further Investigation of a Case of Splenic Atrophy with Calcium and Iron Incrustations (Nodular Splenic Atrophy), Arch. Path. **7**:801 (May) 1929.

5. Jaffe, R. H.: Die Sichelzellenanämie, Virchows Arch. f. path. Anat. **265**: 452, 1927.

6. Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia. Two Cases, One with Necropsy, Am. J. Dis. Child. **26**:132 (Aug.) 1923.

7. Steinberg, B.: Sickle Cell Anemia, Arch. Path. **9**:876 (April) 1930.

8. Rich, A. R.: The Splenic Lesion in Sickle Cell Anemia, Bull. Johns Hopkins Hosp. **43**:398 (Dec.) 1928.

than a contraindication for the procedure, and that it is irrational to withhold operation in cases in which the spleen is not palpable. Sydenstricker[9] expressed his opinion thus: "The benefit derived from the operation has varied directly with the size of the spleen; where there was marked splenomegaly improvement has been considerable; where the spleen was small, the results have been discouraging." Musser and Wintrobe,[10] stated that "this method of treatment is still in the experimental state. Improvement has been noted, particularly in those infants in whom splenomegaly was present." Yater and Mollari[11] advocated splenectomy in active cases as early as possible.

Graham and McCarthy,[12] Steinberg,[7] and Leivy and Schnabel[2f] in recent publications stated that there is little favorable evidence for splenectomy, and that whatever improvement has followed has at best been only temporary. The effects of splenectomy on hemolysis and anemia as revealed by the values in serum bilirubin, erythrocytes and hemoglobin are summarized in graphic form (fig. 5). Leivy and Schnabel's case is omitted because the postoperative data were not published, an entire lack of improvement, however, being noted. In Hahn and Gillespie's case it is possible that there was permanent improvement, but the postoperative follow-up was only of one month's duration. In the cases of Bell and others, Cooley and Lee, and Hahn, there was temporary improvement of varying degree and duration, but in Bell's case there was a severe remission at the end of six months. In Stewart's case, the only one in the series in which there was a small spleen, the patient was not benefited by the procedure, nor was Landon and Lyman's patient, in whom the removed spleen weighed 640 Gm. (in a 6 year old child). All cases which were followed for as long as two months after operation showed no striking improvement; on the contrary, the fluctuations in the erythrocyte counts and hemoglobin continued as in active sickle cell anemia. In addition, no constant or significant changes were noted in the leukocytes, nucleated red blood cells, reticulocytes or fragility, and in no case was there a permanent alteration in the sickle cell trait.

Clinical improvement was noted in three cases.[13] In three cases the abdominal crises recurred.[14] There was no operative mortality.

---

9. Sydenstricker, V. P., in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1930, vol. 2, p. 849.

10. Musser, J. H., and Wintrobe, M. M., in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1931, vol. 6, p. 844.

11. Yater, W. M., and Mollari, M.: The Pathology of Sickle Cell Anemia. Report of a Case with Death During an Abdominal Crisis, J. A. M. A. **96**:1671 (May 16) 1931.

12. Graham, G. S., and McCarthy, Sarah H.: Sickle Cell (Menisocytic) Anemia, South. M. J. **23**:598 (July) 1930.

13. Footnote *2a*, *c* and *d*.

14. Footnote *2b*, *e* and *f*.

It is manifest that the cases have been too few, the age group too limited and the preoperative and postoperative data too meager to allow a fair appraisal of the procedure. In the interpretations of the results as recorded, the effects of other therapeutic measures, such as transfusion and hospital care, have not been given due consideration. More important still is the fact that spontaneous remissions are characteristic of sickle cell anemia. In the case reported in this article there was definite clinical and hematologic improvement on the first two admissions.

On the basis of the recorded evidence, it is our opinion that the benefits of splenectomy have not yet been proved. If the procedure is to be given further trial, it should be on an experimental basis, and attempted only in cases in which the spleen is enlarged. The removal of small spleens may not only be valueless, but it may be, as in our case, impossible, and may impose on the patient an additional operative risk. In all cases of adults and of some children with active sickle cell anemia in which autopsy observations have been reported the spleen has been small.

SUMMARY AND CONCLUSIONS

1. A case of active sickle cell anemia is reported in an adult on whom splenectomy was attempted; a complete autopsy was performed.

2. An analysis of the literature in regard to splenectomy reveals that permanent benefit following the procedures has not been proved.

3. The fibrosis and atrophy of the spleen in chronic cases of sickle cell anemia establish a definite contraindication for splenectomy in adults.

Mr. Joseph L. Scianni, artist, Pathological Institute, University of Tennessee, made the photomicrographs.

NOURISHMENT OF THE MYOCARDIUM THROUGH THEBESIAN VESSELS

IN A HEART IN WHICH THE LARGE CORONARY ARTERIES AND VEINS WERE DESTROYED BY TUBERCULOUS MYOCARDITIS

SAMUEL BELLET, M.D.

B. A. GOULEY, M.D.

AND

THOMAS M. McMILLAN, M.D.

PHILADELPHIA

Interest in the thebesian vessels or sinusoids has been renewed to a considerable degree in recent years. Pratt,[1] Kretz [2] and Wearn,[3] particularly, have studied these vessels, and have expressed the belief that the heart can be effectively nourished through these channels after both coronary arteries have been occluded. Leary and Wearn [4] further believe that under such conditions the only source of blood supply to the myocardium is through these channels.

Although several instances of occlusion of both coronary arteries have been reported [5] in which a thebesian circulation was assumed, in no such case, so far as we know, have the sinusoids or dilated thebesian channels been investigated histologically and their distribution and other features studied. The heart of a boy, aged 16, described in case 5 in a paper on "Tuberculosis of the Myocardium," [5b] presented a certain combination of pathologic changes which make it appear that for a period, at least, the main body of the ventricles was nourished solely by the thebesian vessels. We wish to present the pathologic and histologic evidences on which this opinion is based.

From the Division of Cardiology and Pathology of the Philadelphia General Hospital and the Robinette Foundation of the University of Pennsylvania.

1. Pratt, J. H.: The Nutrition of the Heart Through the Vessels of Thebesius and the Coronary Veins, Am. J. Physiol. **1**:92, 1898.

2. Kretz, J.: Ueber die Bedeutung der Venae minimae thebesii fur die Blutversorgung des Herzmuskels, Virchows Arch. f. path. Anat. **266**:647, 1927.

3. Wearn, J. T.: The Rôle of the Thebesian Vessels in the Circulation of the Heart, J. Exper. Med. **47**:293, 1928.

4. Leary, T., and Wearn, J. T.: Two Cases of Complete Occlusion of Both Coronary Orifices, Am. Heart J. **5**:412, 1930.

5. (*a*) Allbutt, Clifford: Diseases of the Heart, Including Angina Pectoris, London, The Macmillan Company, 1915, vol. 2, p. 21. (*b*) Batson, O. V., and Bellet, S.: The Reversal of Flow in the Cardiac Veins, Am. Heart J. **6**:206, 1930. (*c*) Cabot, R. C., and Mallory: Case 16001: Pain Between the Thyroid and Xyphoid, New England J. Med. **202**:287, 1930. (*d*) Leary and Wearn.[4]

The large coronary arteries were completely occluded a short distance from their origin by tuberculous intimal involvement and by compression from a surrounding caseous tumor.[6] The medium-sized arteries were also destroyed.[7] Occasional arterioles near the endocardium were found to be patulous, but so far as we could determine, the destruction proximally of the larger arteries prevented these small arterioles from receiving blood through the usual channels. The large veins were affected to an even greater degree than were the arteries, the surface vessels being entirely destroyed. In the inner half of the myocardium where caseation had not destroyed them, large dilated veins with thickened walls were found. The coronary sinus and the main vein leading to it were considerably dilated over a distance of ¾ of an inch (1.9 cm.). At this point, however, the vein became entirely occluded by the tuberculous process, there being, therefore, no way for the blood to enter or to leave the right auricle through the coronary veins.

In this heart, therefore, a condition existed in which at best only the auricular muscle and a small portion of the ventricular muscle could have received any blood through arteries. Moreover, reversal of blood flow through the coronary sinus and veins, a mechanism which Batson and Bellet[8] believe under certain circumstances may be important in the nourishment of the myocardium, could not have been active, at least in the final stages, because of destruction of the main coronary veins and the closure of the coronary sinus. It is difficult, therefore, to avoid the conclusion that the undestroyed ventricular muscle in this case, in its terminal stages at least, received its nutrition entirely through a thebesian circulation.

PATHOLOGIC OBSERVATIONS

The heart was exhaustively studied by means of serial section made from various portions. Sections from the ventricles showed the right ventricle to be relatively less involved by tuberculosis than the left, the walls of the latter being almost entirely caseous, except for a narrow subendocardial zone, where the myocardium had been preserved.

The wall of the right ventricle contained an amazing number of vascular spaces or sinusoidal channels; relatively few were present in the muscle of the left ventricle (compare figures 1 to 6 with figure 7). The sinusoidal spaces near the endocardium were on the whole more

6. Gouley, B. A.; Bellet, S., and McMillan, T. M.: Tuberculosis of the Myocardium: A Report of Six Cases with Observations on Tuberculous Involvement of the Coronary Arteries, Arch. Int. Med., to be published.

7. The auricular coronary branches arising from the proximal undestroyed portions of the coronary arteries were patent.

8. Batson and Bellet.[5d]

numerous and larger than those deep in the muscle. Their walls likewise were thicker and more highly organized, being composed of a relatively thick outer fibrous wall, lined by endothelium, while the smaller intramural ramifications often possessed a wall of no more than a single layer of endothelium.

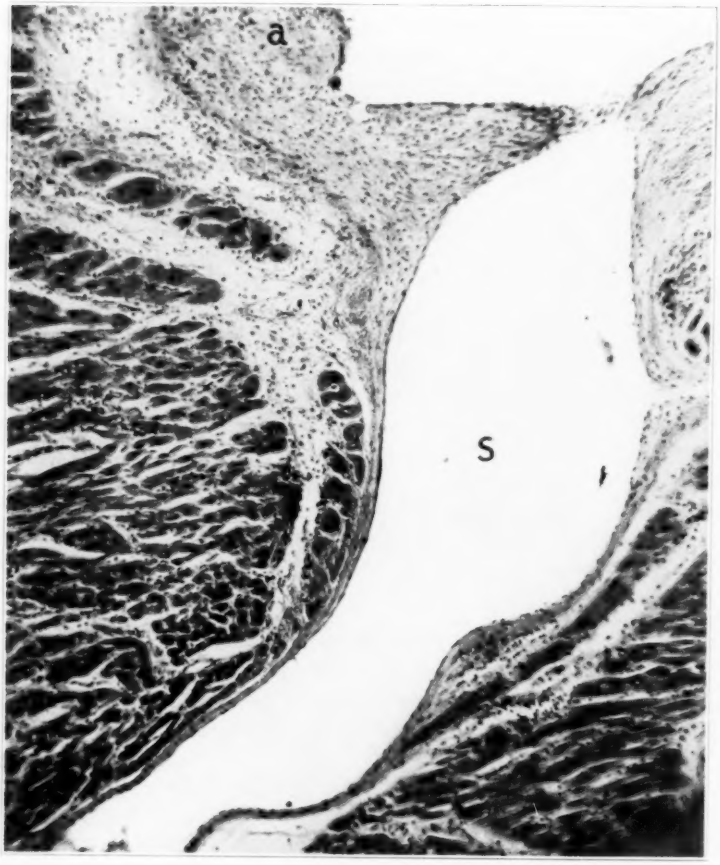


Fig. 1.—Sinusoid within the myocardium. Large saccular sinusoid (*S*) with irregular fibrous thickening of the wall. Part of this thickening (*a*) may be due to tuberculous infiltration; × 60.

The diminution in size of these vessels as they penetrated the interior of the muscle was not always a gradual or progressive change, sinusoids frequently maintaining the caliber of larger medium-sized veins until they became united with such vessels. Not infrequently,

large sinusoids with fibrous walls suddenly became narrowed, giving the appearance of sacculation; beyond this constriction the channels often showed sudden increase in size, leading to one or more thin-walled spaces; this formation suggested that the latter thin-walled dilatation may at times have exercised a sort of reservoir function and acted to retain blood within the myocardium during certain phases of the cardiac cycle, the narrowing and sacculation aiding by exercising a sort of valvular mechanism (fig. 1).

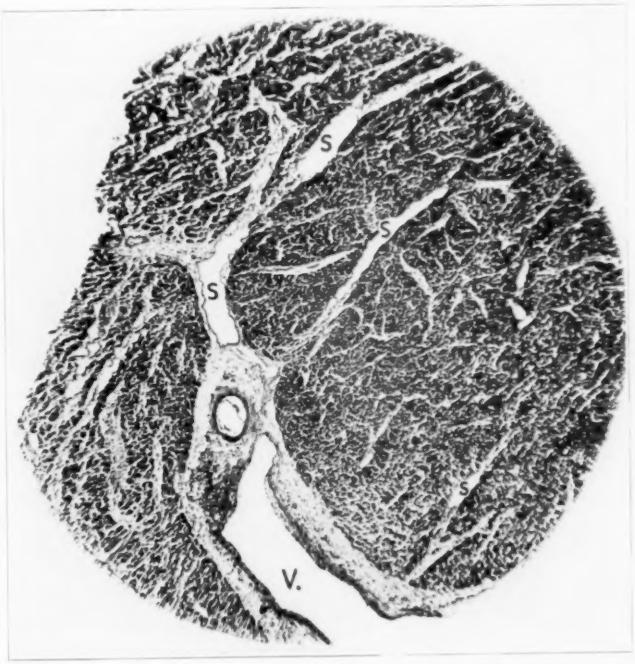


Fig. 2.—Low power view of a large dilated vein (*V*) and numerous sinusoids (*S*) branching into the myocardium. Their connections with veins (*V*) were traced by serial sections; × 30.

These thin-walled sinusoidal vessels could be traced from the endocardium to the larger veins in the depth of the cardiac muscle, with which they communicated directly and freely. On the other hand, communication with the arterial system was difficult to follow. Capillaries leading from some of the smaller arterioles could be traced to the sinusoids, but only after a comparatively long and tortuous course. This makes us unwilling to say that the occasional undestroyed arteriole may not have participated to some extent in the circulation.

We are certain, however, that in the end-stages they were not connected with large arteries, and that their only connection was with sinusoids by means of infrequent small tortuous capillaries, which we do not believe were sufficient to furnish an effective amount of blood to the undestroyed arterioles. That these remaining arterioles did not function efficiently is also indicated by the fact that in many of them remnants of endothelial débris could be seen. In figure 6, an

Fig. 3.—Dilated thin-walled sinusoids (*S*) in the depth of the myocardium. These can be traced to a large subendocardial sinusoid and to the vein seen in figure 2. Note the obliterated artery (*A*); × 57.

arteriothebesian connection is shown; the relative size of the capillary connection can be judged by comparing it with the arteriole and sinusoid shown.

The differentiation between veins and large sinusoids was often difficult and sometimes impossible. When the fibrous walls contained some remnant of smooth muscle, the identification was simple. In a number of instances, a gradual transition from vein to sinusoid was present; what appeared to be a vein in one section could be classed as a sinusoid in the next. In one section, illustrated in figure 5, the

wall of the vessel shows the histologic evidence of a vein in one segment and a sinusoid in the rest of the circumference. Red blood cells were observed in many of the sinusoids.

Elastic tissue stains (Weigert) brought out the surprising fact that the normally small amount of elastic tissue observed in the venous walls was continued throughout the anastomoses and transitions until the endocardium was reached. Large thin-walled spaces under the

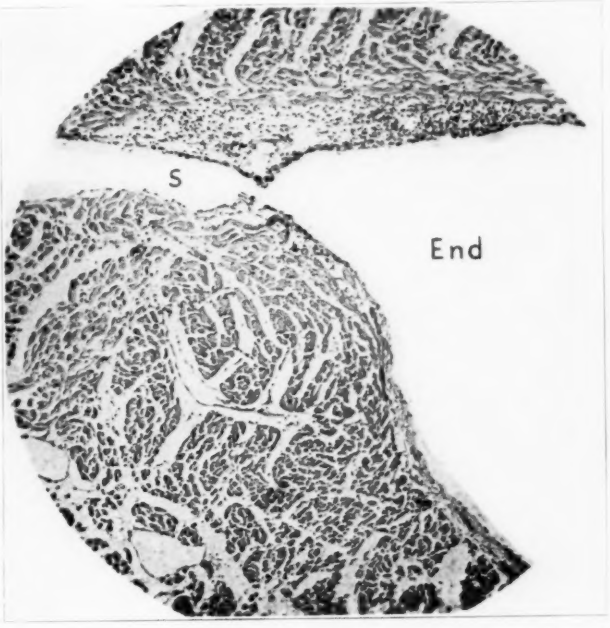


Fig. 4.—The opening of a sinusoid (*S*) into the endocardium (*End*). Note the endocardial thickening with a cribriform constriction at the mouth of the sinusoid. × 62.

myocardium and also the so-called "communicating pits" contained thin strands of elastic tissue.

COMMENT

It should be recalled that at least from one half to two thirds of the right, and three fourths of the outer portion of the left, ventricular wall were destroyed by the caseous process. A sinusoidovenous circulation sufficiently nourished this small portion of the ventricular wall to support life for a relatively considerable period. How efficiently such a system would have maintained a circulation in ventricular walls

of normal thickness is not shown by our case. The relatively few sinusoids in the remaining left ventricular wall in a heart in which this system was developed most probably to a maximum make it somewhat difficult to see how a left ventricular wall of normal thickness could be adequately nourished by such a mechanism alone. In this connection it should be remembered that the thebesian vessels were more numerous subendocardially and progressively became smaller and less numerous toward the outer portions of the ventricular walls.

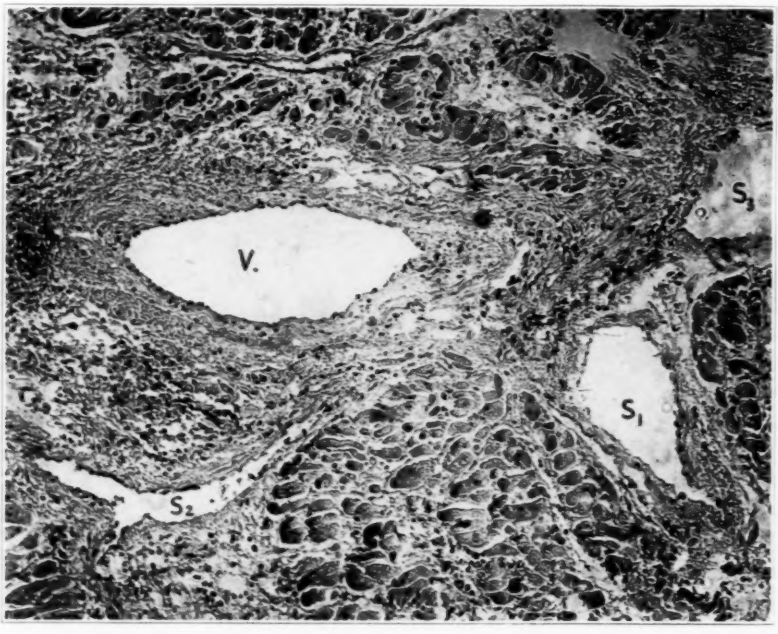


Fig. 5.—A vein (V) with a number of branching sinusoids (S_1, S_2 and S_3). The venous wall contains definite smooth muscle structure, whereas the sinusoids do not, except S_2, which shows the transition from the venous to the sinusoid formation; a segment of its wall is thicker, contains an occasional smooth muscle nucleus and merges directly with the vein at a slightly lower level; × 100.

This fact suggests that before its destruction by tuberculosis, the outer left ventricular wall had a system of thebesian vessels inadequate to its circulatory needs. Circulatory insufficiency, therefore, may have been a factor in the disproportionately greater destruction of the left ventricular myocardium.

The Mechanism of the Dilatation of the Thebesian Vessels.—Three possible factors may have played a rôle in the dilatation of these

potential thebesian channels: (1) intraventricular tension, (2) intra-auricular tension or (3) intra-arterial tension. Any discussion of the rôle of these factors must be regarded as hypothetic. We wish, however, to discuss the possible part played by the intra-arterial pressure, because we have certain direct pathologic evidence which suggests that this was an important, if not the primary, means by which these channels became dilated. Of the vessels affected by the tuberculous process, the surface veins apparently suffered first. This seems probable because of the thinness of their walls and the comparatively lower pressure in

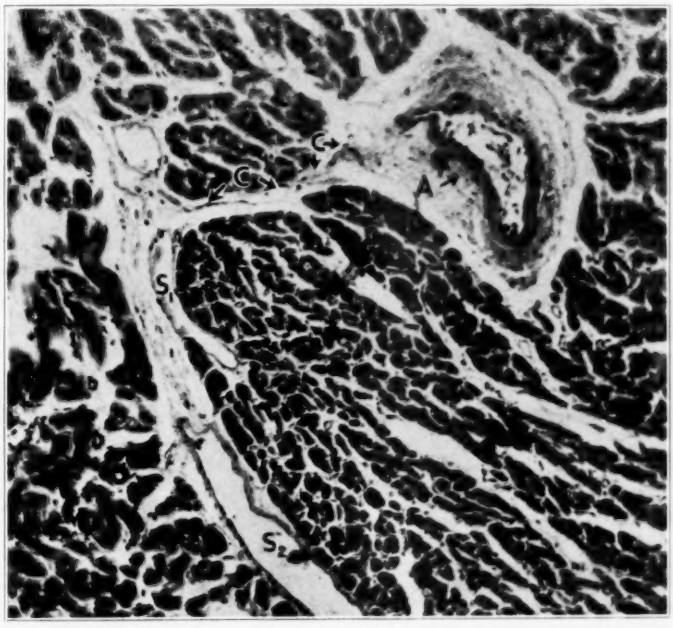


Fig. 6.—Arteriolar-sinusoid communication via capillary (*c*). S_2 leads directly to the endocardium. Such communications were only by means of capillaries; × 100.

the venous system, and also because of the fact that although the proximal portion of the great surface arteries were occasionally observed, the accompanying veins were found to have been completely destroyed. With closure of the surface veins and, later, of the coronary sinus, the arterial blood was forced to seek new channels of egress, the only other outlets being thebesian vessels emptying into the right auricle and right ventricle and, to a lesser extent, into the left ventricle. The portion of the intramural venous system as yet not

engulfed in the process of caseation was under increasing pressure, the vessels constantly enlarging to accommodate the diverted venous blood. Later, after complete closure of the large coronary arteries and reduction of the coronary arterial pressure to practically zero, these dilated sinusoidovenous channels served as the only means of nourishing the myocardium. Leaving aside theoretical considerations of the manner of the original dilatation of these channels, intraventricular

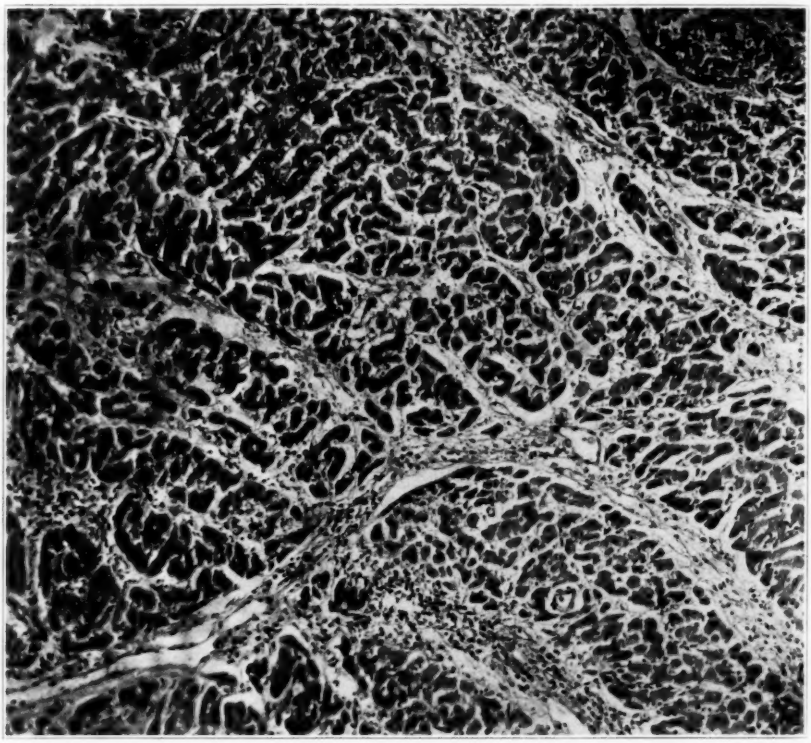


Fig. 7.—A section from the narrow zone of the remaining intact myocardium of the tuberculous left ventricle; tuberculous sinusoids, while present, are relatively few as compared with the numbers seen in the previous photographs taken from the right ventricular sections; × 100.

tension was sufficient to maintain a circulation through these dilated sinusoidovenous channels after the pathologic changes were fully developed. We believe that the circulation occurred by an ebb-and-flow effect. Our case furnishes no data as to whether blood entered the myocardium during diastole or during systole.

Arteriothebesian Anastomoses.—Wearn[9] expressed the belief that there exist relatively large and free connections between arteries and thebesian vessels. This belief has not been confirmed by the injection and histologic studies of Grant and Viko,[9] nor by the work of Stella,[10] who employed physiologic methods. In the case we describe, there undoubtedly were arteriothebesian connections. These, however, were infrequent and were of no higher order than small capillaries; the arterial side of this connection was never larger than a small arteriole (fig. 6). It seems unlikely, therefore, that the thebesian-arterial connections were a potent factor in the nourishment of this heart.

CONCLUSIONS

The heart of a 16 year old boy is described in which an unusual degree of tuberculous fibrocaseous infiltration had destroyed the coronary arteries and the large surface veins. A system of sinusoids (thebesian vessels), many of which were dilated and some of which had thickened walls, connected the endocardium with remaining intramural veins and furnished the only means of myocardial nourishment.

The unusual pathologic cause of the obliteration of the coronary circulation (both arteries and veins) prevents a direct and exact comparison of the circulatory features of the heart described with those seen in double coronary occlusion of the more chronic types.

9. Grant, R. T., and Viko, L. E.: Observations on the Anatomy of the Thebesian Vessels of the Heart, Heart **15**:103, 1929.

10. Stella, G.: The Part Played by the Thebesian Vessels in the Blood Supply to the Heart, J. Physiol. **73**:36, 1931.

TREATMENT OF ELDERLY DIABETIC PATIENTS WITH CARDIOVASCULAR DISEASE

AVAILABLE CARBOHYDRATE AND THE BLOOD SUGAR LEVEL

SAMUEL SOSKIN, M.D.

LOUIS N. KATZ, M.D.

SOLOMON STROUSE, M.D.

AND

SAMUEL H. RUBINFELD, M.D.

CHICAGO

The greater incidence of arteriosclerosis in diabetic patients and the younger age groups in which it occurs have long been recognized. More recently diabetes has come to be regarded as one of the important causes of angina pectoris. With the advent of insulin, the prolongation of diabetic life, especially as regards children, has rendered the problem of this form of cardiovascular disease more pressing.

The etiologic relationship between diabetes and cardiovascular disease and the problem involved in the treatment of these allied conditions have been the subjects of much speculation with but a slow advance in knowledge. The introduction of insulin has not made matters much clearer. On the contrary, the more rigid control of the metabolic disturbance made possible by the use of this hormone has made it evident that during the rigorous treatment of the diabetic symptoms, the cardiovascular status of the patient may not only remain unimproved, but may often be appreciably influenced in an adverse direction. The literature contains many references, both clinical and experimental, to the deleterious effects of insulin shock on the myocardium. The reports vary from the precipitation of decompensation or anginal attacks in diabetic patients with a damaged myocardium, to actual fatalities preceded by such phenomena. More recently electrocardiographic studies have been made with the view of gaining a more intimate knowledge of the effect of insulin hypoglycemia on the heart. The recent paper of Middleton and Oatway [1] (which contains an excellent bibliography of the afore-

From the Max Pam Metabolism Unit, the Heart Station and the Department of Physiology, Michael Reese Hospital.

Aided by the Max Pam Fund for the Study of Metabolic Diseases, and the Emil and Fanny Wedeles Fund for the Study of Diseases of the Heart and Circulation.

1. Middleton, W. S., and Oatway, W. H.: Insulin Shock and the Myocardium, Am. J. M. Sc. **181**:39, 1931.

mentioned literature) reports a series of such observations. The chief electrocardiographic variation that they observed was, in confirmation of previous workers, a flattening or inversion of the T wave. Other less constant findings were an increase in the A-V conduction time and a depressed P wave. These observations are also in agreement with the results of electrocardiographic studies by Wittgenstein and Mendel,[2] by von Haynal [3] and by others on the hearts of lower mammals.

There can be no doubt that insulin hypoglycemia represents a definite and characteristic insult to the myocardium. Middleton and Oatway,[1] however, reported similar though less marked results in four cases in which the insulin did not lower the blood sugar below 70 mg. per hundred cubic centimeters. These results seem to lend support to the opinions of von Haynal, Vidovszky and Györgi [4] and of Schäffer, Bucka and Friedländer,[5] that the electrocardiographic changes are due to a direct action of insulin (or a component) on the heart, rather than to the accompanying hypoglycemia. One of us (J. Soskin [6]) has recently shown that the diabetic organism as a whole suffers little if any impairment in its ability to oxidize carbohydrate. The difficulties involved in the determination of the utilization of carbohydrate by the isolated diabetic heart have led to contrary reports and conclusions.[7] When it is remembered, however, that few if any of the diabetic patients under consideration are completely diabetic, it must be realized that the carbohydrate requirement of their hearts cannot be disregarded. Furthermore, as Middleton and Oatway [1] pointed out, none of their patients had hearts that could be considered normal. In view of the work of Smith, Gibson and Ross [8] and of others on the beneficial effects of high carbohydrate diets in the relief of congestive heart failure, it seems likely that the pathologic heart requires a greater amount of carbohydrate than the normal heart. This may account for the results of

2. Wittgenstein, A., and Mendel, B.: Die Veränderung der T-Zacke des Electrokardiograms wärhend der Insulinwirkung, Klin. Wchnschr. **3**:1119, 1924.

3. von Haynal, E.: Electrokardiographische Untersuchungen über Insulinwirkung auf das Herz: II., Klin. Wchnschr. **4**:1729, 1925.

4. von Haynal, E.; Vidovszky, L., and Györgi, G.: Electrokardiographische Untersuchungen über Insulinwirkung auf das Herz., Klin. Wchnschr. **7**:1543, 1928.

5. Schäffer, H.; Bucka, E., and Friedländer, K.: Ueber die Einwirkung des Insulin und der Hypoglykämie auf das menschliche Herz, Ztschr. f. d. ges. exper. Med. **57**:35, 1927.

6. Soskin, S.: The Utilization of Carbohydrate by Totally Depancreatized Dogs Receiving no Insulin, J. Nutrition **3**:99, 1930.

7. Cruickshank, E. W. H., and Shrivastava, D. L.: The Action of Insulin on the Storage and Utilization of Sugar by the Isolated Normal and Diabetic Heart, Am. J. Physiol. **92**:144, 1930.

8. Smith, F. M.; Gibson, R. B., and Ross, N. G.: The Diet in the Treatment of Cardiac Failure, J. A. M. A. **88**:1943 (June 18) 1927.

Middleton and Oatway[1] on insulin without hypoglycemia, since the blood sugars of their patients, although not abnormally low for the normal heart, may represent a state of relative hypoglycemia for the diseased myocardium. A similar explanation may apply to the work of Parsonnet and Hyman,[2] who observed the development of the stenocardial syndrome in diabetic patients with old coronary thrombosis, following doses of insulin that did not produce hypoglycemia.

It was with particular reference to these latter considerations that the work here presented was undertaken. If insulin exerts a direct deleterious action on the myocardium, then its continued administration to diabetic patients with cardiovascular disease, even though never sufficient to produce hypoglycemia in the usual sense, must be viewed with some apprehension. If, on the other hand, the hypoglycemia, whether absolute or relative, is responsible for the cardiac embarrassment, then the diet accompanying the insulin must be of paramount importance. In the following experiments we have attempted to evaluate the influence of insulin and of diet on the cardiovascular status of elderly diabetic patients with cardiovascular disease.

METHODS

Seven elderly diabetic patients with clinical evidence of coronary sclerosis or angina pectoris were studied. These patients remained in the Max Pam Metabolism Unit throughout the entire period of each experiment. Six patients were kept for from two to four weeks on accurately controlled diets which permitted their accustomed high blood sugar level and glycosuria, no attempt being made to control the diabetic manifestations to a greater extent than was usual with each patient before entrance to the hospital. This period was followed by a similar period in which the diet remained unchanged but insulin was used in therapeutic doses. During the latter period the blood sugar was kept at a low normal level, but at no time was sufficient insulin given to produce persistent hypoglycemia. One patient with mild diabetes, who was particularly suitable for the purpose, was given no insulin throughout the experiment, her diabetic manifestations being controlled by diet alone. For this patient alternating periods of high and low carbohydrate diet were used.

In addition to the usual clinical observation and the routine daily urinalysis of these patients, quantitative twenty-four hour determinations of the excretion of dextrose and nitrogen in the urine and the fasting blood sugar level were determined daily. The blood cholesterol and the carbon dioxide content of the venous blood were determined twice a week. Observation of the cardiovascular system was limited to daily measurements of the blood pressure and pulse rate and the recording of electrocardiograms twice a week. A great many additional electrocardiograms and related observations were made at various times when the patients manifested unusual symptoms or complained of untoward subjective states. Further experiments, which will include observations on the peripheral vascular system, are projected.

2. Parsonnet, A. E., and Hyman, A. S.: Insulin Angina, Ann. Int. Med. **4**: 1247, 1931.

As a basis for comparison with previous studies, each of our patients was subjected to one or more acute experiments. After a control period of observation, a single large dose of insulin was administered. The pulse rate, respiratory rate, arterial blood pressure, blood sugar level and electrocardiogram were determined at frequent intervals before and after the administration of the insulin. After sufficient time had elapsed for the development of a significant hypoglycemia, dextrose was administered intravenously and by mouth, and the observations were continued.

RESULTS OF ACUTE EXPERIMENTS

The results obtained in the acute experiments are presented herewith first both because the phenomena observed were of greater magnitude than those obtained in the therapeutic experiments and because they are necessary for the interpretation of the latter. These acute experiments differ from most of those previously reported in that the administration of an overdose of insulin was given after the patients had been observed under controlled conditions over relatively long periods of time. This procedure enabled us to procure several observations: while the patient was comfortably at rest before receiving insulin, during the development of hypoglycemia after the administration of insulin and during the recovery from hypoglycemia following the administration of sugar.

Typical acute experiments are shown in the summary protocols (figs. 1 and 2). For purposes of brevity and clarity, the results in these protocols and others are summarized under the appropriate subheadings.

Respiration and Blood Pressure.—No significant change in respiratory rate was observed. The blood pressure tended to drop during the course of action of insulin. Thus, the systolic and pulse pressures dropped in five of nine experiments (fig. 1), remained practically unchanged in two and rose in two experiments. The rise in blood pressure in one of the latter experiments was associated with an attack of paroxysmal auricular fibrillation (fig. 2). The diastolic pressure fell in four of nine experiments (fig. 2), remained unchanged in four, and temporarily rose in one (fig. 1). After the administration of sugar there was in many cases a tendency for the blood pressure to be restored toward normal. However, the experiments shown in figures 1 and 2 are exceptions and fail to show this restoration. The tendency for the administration of sugar to restore the blood pressure level favors the view that insulin rather than rest in bed during the experiment was chiefly responsible for the previous drop in blood pressure. It was observed that whenever patients became uncomfortable or apprehensive there was a temporary rise in blood pressure. Thus, in many cases, when the symptoms of insulin shock became marked, a rise in blood pressure was seen. A temporary rise in blood pressure often occurred when the insulin or sugar solution was injected (viz., effect of sugar solution in fig. 1).

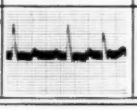
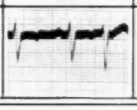
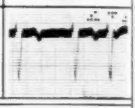
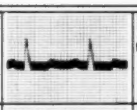
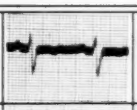
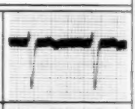
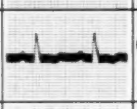
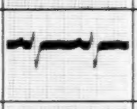
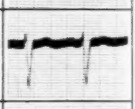
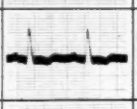
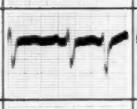
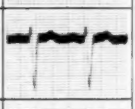
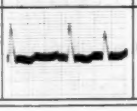
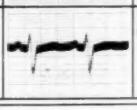
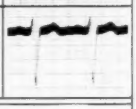
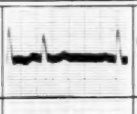
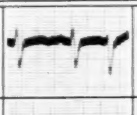
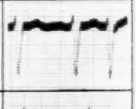
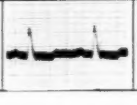
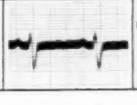
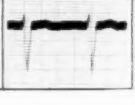
TIME		PULSE RATE	RESP^{N} RATE	ART. BLOOD PRESS.	BLOOD SUGAR	ELECTROCARDIOGRAMS		
						LEAD I	LEAD II	LEAD III
P M 1:45	RESTING COMFORTABLY	PER MIN. 84	PER MIN. 18	MMS. HG. 152/60	MGMS.% 296			
2:00	40 UNITS INSULIN INJECTED SUBCUTANEOUSLY							
2:30	NO COMPLAINTS	76	18	135/73	204			
3:00	NO COMPLAINTS	86	18	138/78	206			
3:40	TRIGEMINAL PULSE AT WRIST	88	17	125/60	106			
4:30	COMPLAINS OF HUNGER	80	18	118/64	44			
4:38-4:43	50 C.C. OF 50% GLUCOSE INJECTED INTRAVENOUSLY							
4:50	PERSPIRING; COMPLAINS OF HUNGER	76	18	128/60	190			
5:40	TRIGEMINUS NOT PALPABLE HUNGER DIMINISHED	88	18	118/62	72			

Fig. 1.—Summary protocol of acute experiment on Harry S.

Our series offers as much variability in the changes in the blood pressure following the administration of insulin as reported in the literature (Middleton and Oatway [1]), but on the whole our results show that aside from the effects of subjective distress, the blood pressure—systolic, diastolic and pulse—tends to fall during insulin hypoglycemia.

Heart Rate and Rhythm.—The changes in heart rate, like the changes in blood pressure, were variable. Similar variability was reported in the literature (Middleton and Oatway [1]). In three experiments the rate fell during the insulin effect; in five experiments the rate increased (in two of the latter the change occurred only during insulin shock), while in one experiment the rate remained unchanged (fig. 1). It is interesting to note that in the case shown in figure 2 there was an increase in rate before the cardiac mechanism changed. The administration of sugar did not always restore the rate to normal. Just as in the case of the blood pressure, the changes in heart rate are complicated by the effects of psychic distress.

Several changes in the mechanism of the heart were observed. A striking sinus arrhythmia developed in one patient at the point of maximum hypoglycemia. The slowing of the heart rate and sinus arrhythmia may be due to a direct action on the sinus node or to an influence on the vagus nerves, either centrally or peripherally. The inconstancy of the results indicates that other mechanisms, such as reflex acceleration following lowering of the blood pressure, may also operate.

Insulin apparently increases the irritability of ectopic foci. Extrasystoles developed in three cases, the origins being auricular, ventricular (fig. 2, 1:40) and nodal, respectively. In a second experiment on the patient in figure 1, the extrasystoles that were present at the start were increased in frequency during the insulin period. The administration of sugar caused a disappearance of the ectopic rhythm, except in the last mentioned experiment, in which their frequency was reduced. Similar changes have been reported by others, especially Schäffer, Bucka and Friedländer,[5] who also noted the occurrence of auricular fibrillation. A striking instance of paroxysmal auricular fibrillation accompanied by a typical attack of angina pectoris was found in the patient whose protocol is shown in figure 2. This mechanism was temporarily converted to a sinus tachycardia after the administration of sugar intravenously (fig. 2, 2:45), coincident with the relief of the angina pectoris. This last change could not have been diagnosed without the electrocardiogram, because the irregular pulse deficit at the wrist persisted. Auricular fibrillation, however, soon returned without the angina and lasted until the next morning.

Symptomatic Changes.—In addition to the occurrence of some or all of the typical symptoms of insulin shock, typical attacks of angina

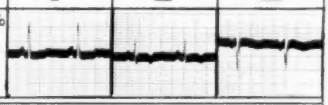
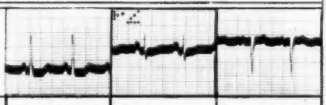
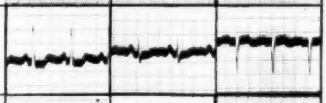
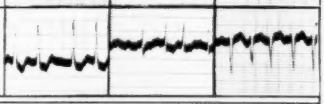
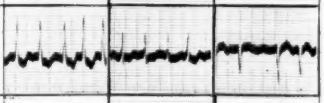
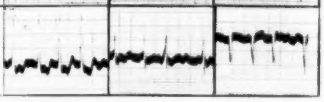
TIME		PULSE RATE	RESPN RATE	ART. BLOOD PRESS.	BLOOD SUGAR	ELECTROCARDIOGRAMS		
						LEAD I	LEAD II	LEAD III
P.M. 12:40	RESTING COMFORTABLY	PER MIN. 72	PER MIN. 24	MMS. HG 184/106	MGMS. % 56			
12:50	25 UNITS INSULIN INJECTED SUBCUTANEOUSLY							
1:10		112	24	180/100	52			
1:30	COMPLAINS OF THIRST	112	24	212/90	68			
1:40	AURICULAR FIBRILLATION AUSCULTATED 1:35 COMPLAINS OF PRECORDIAL PAIN	96	24	212/80	36			
2:10	PRECORDIAL PAIN RADIATING TO LEFT ARM INCREASING THIRST	115-125	26	200/90	27			
2:15-2:20	3 OUNCES ORANGE JUICE + 3 TEASPOONSFUL CANE SUGAR TAKEN BY MOUTH							
2:25-2:40	50 CC. OF 50% GLUCOSE INJECTED INTRAVENOUSLY							
2:45	COMPLAINS OF EXTREME FATIGUE NO PAIN	99	26	200/90	107			
3:00	FEELS MUCH BETTER DESIRES TO URINATE	103	26	206/90	110			
4:40	SLEPT FOR FEW MINUTES RESTING COMFORTABLY	104	24	212/100	82			

Fig. 2.—Summary protocol of acute experiment on Lena S.

pectoris developed in two cases. All of these symptoms were relieved after the administration of dextrose.

Electrocardiographic Changes.—P wave and P-R interval. The changes in the P wave were variable. In all but three experiments on two patients it became shorter and more peaked. In the others, it became longer and more notched (fig. 1). The P-R interval remained unchanged in many of the experiments. In one it lengthened slightly (fig. 1); in three, in which the P wave became shorter, it also became shorter.

QRS complex. In all experiments the QRS complex became smaller in one or more leads. In two experiments the QRS complex became more slurred. In two experiments on one patient, in which the QRS complex was at the upper limits of normal, the duration became slightly longer after the administration of insulin (fig. 1). There was a tendency for restitution with the administration of sugar. No axis shift was noticed. These changes in the QRS complex and in the P wave and P-R interval are in accord with the results of previous workers (Middleton and Oatway [1]).

S-T segment and T wave. Much more striking and consistent findings were observed in these portions of the electrocardiogram following the administration of insulin. The changes in the S-T segment and T wave were found to depend on the direction of the major deflection of the QRS complex, a correlation hitherto overlooked. Thus, in lead I, in which the major initial complex was upright, the S-T segment became negative (fig. 3). When the QRS complex was negative to begin with, the deviation of the S-T segment from the iso-electric level increased, and it changed from a horizontal to a descending line (figs. 1 and 2). In the few cases in which the major initial deflection was upright in lead III, the S-T segment in that lead became negative. In most cases, however, the major deflection of the QRS complex was inverted in lead III, and the S-T segment in this lead became positive (fig. 3) or its deviation above the iso-electric line increased, and at the same time it tended to change from a horizontal to an ascending line (figs. 1 and 2). While the changes in the S-T segment in lead II fell into the same category, they were less striking, and exceptions occurred in two cases in which the amplitude of the QRS complex was small. Thus, in figures 1 and 2 the changes were as anticipated, while in figure 3 there was no shift in the S-T segment.

The T wave in lead I, which in our series was upright in all cases to start with, became flatter, lost its peaklike quality and increased in duration after the administration of insulin (figs. 2 and 3). In two instances it became diphasic (fig. 1), and in one case it became indiscernible. The T wave in lead III started out as a cove-shaped negative wave in the majority of our cases, associated in every instance with an inverted major deflection (figs. 1, 2 and 3). With insulin, the T wave

became less negative, its duration increased, its cove-shaped appearance disappeared, and in some cases it became indiscernible or even upright (figs. 1, 2 and 3). In one experiment, a positive T wave in lead III, associated with an inverted major initial deflection, became larger during the effect of insulin. In two other experiments on another subject, the upright T wave in lead III, associated with an upright major initial deflection, became longer and flatter after the administration of insulin.

The changes in lead II were of a similar nature (fig. 1). However, in two instances (figs 2 and 3) the changes in the T wave were not in line with the other experiments; thus, in one case (fig. 2) a negative T

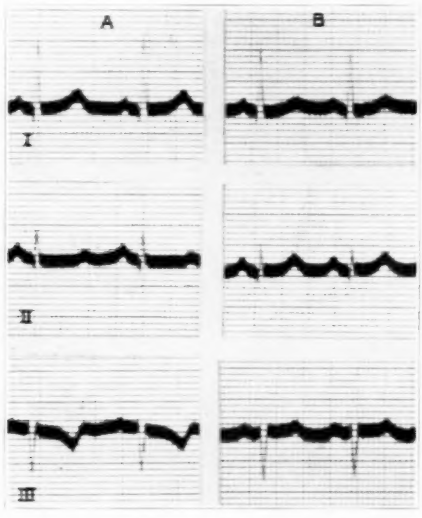


Fig. 3.—Electrocardiograms (three leads), showing effect of insulin on Aaron L. *A* was taken as a control before insulin was given; *B*, after the administration of insulin. Note the reversal of direction from an inverted to an upright T wave in lead III.

wave in lead II, with an upright major initial deflection, became positive, and in the other (fig. 3), an upright T wave in lead II, with an upright major initial complex, became larger. The variability of lead II, as regards both the T wave and the S-T segment, is apparently due to the manner in which the effects in leads I and III summate; it is comparable to the normal variability of these parts of the electrocardiogram in lead III. It follows that in studies similar to this lead I and lead III are of more significance than lead II.

All of the foregoing electrocardiographic changes tended to be restored to the preinsulin status after the administration of dextrose.

RESULTS OF THERAPEUTIC EXPERIMENTS

The details of the therapeutic experiments, except for the electrocardiographic data, are summarized in table 1. Because of limitation of space, the figures presented are averages for the periods indicated. Actual figures for typical days are given in the summary protocols,

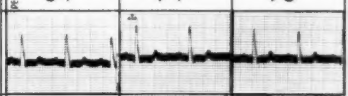
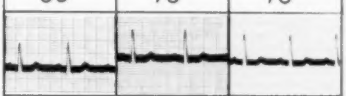
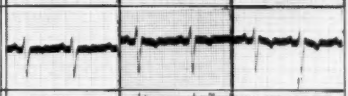
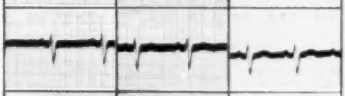
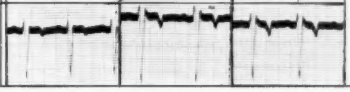
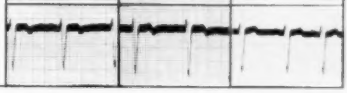
DAY OF EXPT.			2ND	8TH	13TH	INSULIN STARTED ON 19TH DAY	27TH	38TH	40TH
DIET	CHO.	GMS	75	75	75		75	75	75
	FAT	GMS	100	100	100		100	100	100
	PROT.	GMS	50	50	50		50	50	50
	CALS.		1400	1400	1400		1400	1400	1400
AVAILABLE CHO.		GMS.	114	114	114		114	114	114
INSULIN		UNITS	0	0	0		42	46	30
FASTING BLOOD SUGAR		MGMS. %	229	170	250		61	53	133
GLYCOSURIA-24 HR.		GMS	10.2	15.6	15.7		0.48	0.36	2.61
NITROGEN EXCRETION-24 HR.		GMS.	5.97	7.81	7.40		7.33	7.33	4.77
CO_2 CONTENT VENOUS BLOOD		VOLS %	57.1	57.8	56.1		52.7	55.5	52.3
ARTERIAL BLOOD PRESSURE		MMS. HG	150/80	146/80	148/78		154/80	150/80	146/78
PULSE RATE		PER MIN.	84	74	90		88	76	78
ELECTROCARDIOGRAMS	LEAD I								
	LEAD II								
	LEAD III								

Fig. 4.—Summary protocol of typical days during two periods of therapeutic experiment on Harry S.

figs. 4 and 5. The time periods given in table 1 represent periods of consecutive days considered suitable for comparison with other periods. They do not include intermediate periods of adjustment and therefore do not indicate the total length of time necessary for each study.

Great care was taken to keep the intake of food constant throughout the experimental periods. The caloric value of the diets was set at a

low level in order to avoid a masking of their effects by the sheer abundance of energy material. It will be seen, however, that only two of the patients (Esther B. and Ottile P.), who were overweight to begin with, lost any appreciable amount of weight while on experiment. The types of diet used for the various patients varied from moderately low to moderately high carbohydrate mixtures. One patient (Ben S.) differed from the rest in that he received insulin during both experimental periods, the contrast in his case being made between a relatively low and a relatively high administration of insulin while on a constant diet. Another patient (Esther B.) was observed during two cycles, with and without insulin, the diet of one complete cycle being different from that during the other. The last patient (Lena S.) received no insulin whatever throughout her therapeutic experiments, the diet alone being varied from a low to a high carbohydrate mixture.

The chemical data in table 1 show the average extent to which the fasting blood sugar level and the glycosuria varied during the different experimental periods. It may be seen that the fasting blood sugar values did not fall below those ordinarily considered normal, and that some glycosuria usually persisted even during the insulin periods. The figures for the excretion of urinary nitrogen indicate the protein-sparing action during the insulin periods. This was probably due to the retention, during these periods, of dextrose which appeared in the urine in the absence of insulin.

The changes in blood pressure and heart rate which occurred during the insulin periods were slight and inconstant. It is interesting to note that those patients who did show some rise in blood pressure, both systolic and diastolic, during the administration of insulin were receiving the higher carbohydrate diets. In these patients, also, the pulse rate tended to increase. The patients on the lower carbohydrate mixtures showed little or no change in blood pressure and a decrease in pulse rate during the insulin periods. The patient (Lena S.) who did not receive insulin showed a higher blood pressure and a lower pulse rate during the high carbohydrate periods than during the low carbohydrate periods. The effect of insulin on the cardiac rhythm was more definite. It usually increased the incidence of ectopic beats, and in one case (fig. 4) it produced a series of auricular extrasystoles, leading to pulsus trigeminus.

The electrocardiographic changes during the insulin periods were similar to, though of lesser magnitude than, those caused by insulin in the acute experiments (compare figs. 1 and 4). The records obtained during the different periods of the therapeutic experiments were measured for the duration and amplitude of the various phases of the

electrocardiogram. These data were checked by an inspection of the curves to estimate the changes in contour that the measurements failed to reveal.

A comparison of the insulin periods with those periods in which insulin was omitted showed, without exception, one or more of the

DAY OF EXPT.			3RD	13TH	31ST	DIET CHANGED ON 32ND DAY	34TH	45TH	52ND
DIET	CHO.	GMS.	50	50	50		160	160	175
	FAT	GMS.	100	100	100		50	50	55
	PROT.	GMS.	50	50	50		50	50	50
	CALS.		1300	1300	1300		1290	1290	1395
AVAILABLE CHO.		GMS.	89	89	89		194	194	209.5
INSULIN		UNITS	0	0	0		0	0	0
FASTING BLOOD SUGAR		MGMS. %	60	63	93		90	101	75
GLYCOSURIA-24 HR.		GMS.	0.49	0.42	0.34		0.44	0.62	0.37
NITROGEN EXCRETION-24 HR.		GMS.	5.18	4.90	7.51		3.18	4.74	5.22
CO_2 CONTENT VENOUS BLOOD		VOLS. %	55.1	50.4	58.1		49.7	48.5	59.4
ARTERIAL BLOOD PRESSURE		MMS. HG.	140/70	150/70	183/100		187/100	190/95	190/86
PULSE RATE		PER MIN.	80	78	74		66	72	72
ELECTROCARDIOGRAMS	LEAD I								
	LEAD II								
	LEAD III								

Fig. 5.—Summary protocol of typical days, when sinus rhythm was present, during two periods of therapeutic experiment on Lena S.

following changes during the former period: (*a*) a slight prolongation of the P-R interval; (*b*) a slight prolongation of the QRS complex; (*c*) a diminution of the amplitude of the QRS complex in all leads to varying extents; (*d*) a tendency for the S-T interval to shift slightly in the direction opposite to the major initial complex; (*e*) an increase in duration of the T wave; (*f*) an increase in the height of the T wave when it was originally opposite in direction to the major initial complex.

and a decrease in the height of the T wave when it was originally in the same direction as the major initial complex; in several patients (fig. 4) the T wave changed its direction; (*g*) a variable change in amplitude, duration and, sometimes, direction in the P wave.

While these changes are not as striking as those observed in the acute experiments, taken by and large, they are in accord with the changes described in the acute experiments and noted by previous observers. The magnitude of the electrocardiographic deviations induced by insulin did not depend on the absolute level at which the blood sugar was maintained (table 1). Analysis of individual protocols indicated that the length of time over which insulin was administered and the extent of the change from the accustomed blood sugar level to the new level were important factors.

The subjective reactions of our patients to the experimental procedure were in surprising accord with our objective findings. They invariably complained of a decreased sense of well-being during the periods of administration of insulin. The usual complaints were weakness and prostration, dizziness, nervousness, palpitations, precordial pain and constriction, which in some cases (Ottile P., Esther B. and Lena S.) amounted to typical attacks of angina pectoris. Harris I. refused to continue on insulin because he "felt bad all the time."

The therapeutic experiments (Esther B. and Lena S.) in which a comparison of low and high carbohydrate diets was made were particularly informative. The results were similar in both cases. The case of Lena S., who received no insulin except for her acute experiment, deserves special mention. This patient had been treated for her diabetes with a low carbohydrate diet for many months prior to her admission to the Max Pam Unit. A similar initial diet was therefore prescribed for our study (table 1). At this time the patient complained of weakness, evidenced a moderate degree of cardiac decompensation and suffered from attacks of angina pectoris accompanied by paroxysmal auricular fibrillation (fig. 6) from three to four times a week. The substitution of a high carbohydrate diet for the low one produced a startling result. She did not have a single attack of angina pectoris or auricular fibrillation while on the high carbohydrate diet, and her clinical state improved to the extent that we found it difficult to keep her at constant rest in bed. These results were confirmed by repetition. Indeed, her subjective reaction to the second period of low carbohydrate diet was so severe that it had to be cut short. The return to the high carbohydrate diet was again followed by remarkable improvement, her only attack during this period being precipitated when she walked down a long hospital corridor and up several stairs in order to use a telephone.

TABLE 1.—*Summary of Therapeutic Experiments.*

Patient	Comment	Period	Duration, Days	Diet				Insulin, Average Daily Units	Average Fasting Blood Sugar,* Mg. per 100 Cc.	Average Glycosuria, Gm. per 24 Hrs.	Average Urinary Nitrogen, Gm. per 24 Hrs.	Average Morning Blood Pressure, Mm. Hg	Average Morning Pulse Rate, per Min.	Subjective Complaints
				Carbohydrate	Fat	Protein	Calories							
Harry S.	Aged 69, a white man; weight on admission, 45 Kg.; on discharge, 45 Kg.	Control	18	75	100	50	1,400	0	225	13.5	7.9	140/79	91	Euphoria
	Diagnosis: diabetes mellitus; arteriosclerotic heart disease	Insulin	23	75	100	50	1,400	34	80	1.6	7.5	139/78	83	Euphoria
Aaron L.	Aged 44, a white man; weight on admission, 64 Kg.; on discharge, 63 Kg.	Control	11	50	125	50	1,525	0	118	1.0	8.1	155/81	95	Intermittent claudication
	Diagnosis: Diabetes mellitus; arteriosclerotic heart disease; advanced peripheral arteriosclerosis	Insulin	23	50	125	50	1,525	24	70	0.5	6.9	155/84	84	Intermittent claudication
Ottile P.	Aged 61, a white woman, weight on admission, 79 Kg.; on discharge, 74 Kg.	Control	13	150	75	40	1,435	0	152	6.5	6.9	133/75	68	Dyspnea and palpitations
	Diagnosis: Diabetes mellitus; arteriosclerotic heart disease; mild congestive heart failure; obesity	Insulin	21	150	75	40	1,435	28	111	2.0	6.6	137/77	74	Dyspnea and palpitations plus precordial constriction
Harris I.	Aged 64, a white man; weight on admission, 44 Kg.; on discharge, 44 Kg.	Control	18	140	85	65	1,485	0	166	11.6	10.1	109/68	73	No complaints
	Diagnosis: Diabetes mellitus; arteriosclerotic heart disease	Insulin	9	140	85	65	1,485	30	85	0.8	8.4	119/76	80	"Felt bad all the time"
Ben. S.	Aged 68, a white man; weight on admission, 44 Kg.; on discharge, 50 Kg.	Insulin	8	60	120	50	1,520	19	277	38.0	8.7	131/76	80	Dyspnea, swelling of ankles and palpitations
	Diagnosis: Diabetes mellitus; arteriosclerotic heart disease; mild congestive heart failure	More insulin	25	60	120	50	1,520	58	115	3.7	6.0	134/73	74	Dyspnea, swelling of ankles and palpitations
Esther B.	Aged 55, a white woman; weight on admission, 107 Kg.; on discharge, 100 Kg.	Control	15	100	80	60	1,360	0	193	4.3	12.8	104/71	72	Anginal attacks, weakness and swelling of ankles
		Insulin	19	100	80	60	1,360	50	109	3.0	14.8	111/76	72	Increased frequency and severity of angina
	Diagnosis: Diabetes mellitus; rheumatic heart disease; mild congestive heart failure; angina pectoris; obesity	Control	11	75	80	50	1,040	0	192	4.3	12.0	100/65	71	Anginal attacks, weakness and swelling of ankles
		Insulin	13	75	80	50	1,040	55	87	3.2	9.9	109/75	70	Increased frequency and severity of angina
Lena S.	Aged 55, a white woman; on admission, could not be weighed; on discharge, 56 Kg.	Low carbohydrate	31	50	100	50	1,300	0	74	0.5	5.5	165/82	75	Anginal attacks (from 4 to 5 times per week) and weakness
	Diagnosis: Diabetes mellitus;† arteriosclerotic heart disease; moderate congestive heart failure; angina pectoris with paroxysmal auricular fibrillation; nodular goiter	High carbohydrate	32	100	50	50	1,300	0	85	0.5	5.0	188/94	72	No complaints
		Low carbohydrate	8	50	100	50	1,300	0	87	0.7	4.6	196/90	72	Anginal attacks (from 4 to 5 times per week) and weakness
		High carbohydrate	26	200	60	50	1,540	0	107	1.4	4.5	202/100	69	No complaints

* "True" blood sugar values were determined by the Somogyi modification of the Shaffer-Hartmann method, which yields results approximately 20 mg. per hundred cubic centimeters lower than the Folin-Wu method.

† This patient's diabetes was mild, but the following results were obtained in a typical carbohydrate tolerance test: fasting blood sugar level, 86 mg.; 100 Gm. of dextrose by mouth; one-half, one hour and two hours later, the blood sugar levels were 221, 252, and 226 mg. per hundred cubic centimeters, respectively.

The summary protocol in figure 5 shows three typical days from each of the first two experimental periods on this patient. The changes in the electrocardiogram are the same as those already described in the acute and therapeutic experiments with insulin. The depression of the S-T segment in leads I and II and its elevation in lead III during the low carbohydrate diet are striking, as is also the conversion of the negative T wave of lead III to an upright one. The QRS complex in this patient, unlike that in the others, became larger while the patient was on a low carbohydrate diet, a change also noted in her acute experiment with insulin. It is interesting to note that the blood pressure

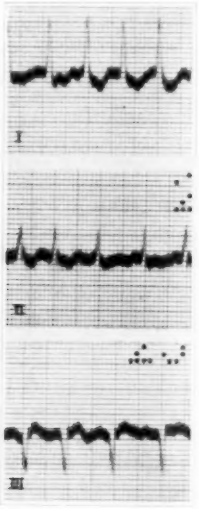


Fig. 6.—Electrocardiogram taken during an attack of paroxysmal auricular fibrillation accompanied by angina pectoris, which appeared during the low carbohydrate period in Lena S.

during the time the patient was on a low carbohydrate diet was lower than that during the time she was on a high carbohydrate diet, and that the pulse rate was faster in the former period. These changes were consistent and may have been associated with the angina and paroxysms of auricular fibrillation. A similar change in blood pressure was also observed in Esther B.

The results with these two patients show that low carbohydrate diets produce the same effects on the heart as are produced by the therapeutic use of insulin. This effect of the low carbohydrate diet is associated with a relatively small change in the blood sugar level. But the greater

amount of carbohydrate readily available to the damaged myocardium in the high carbohydrate diet would seem to be the significant factor for the well-being of these patients. This is in accord with the recent studies of Smith and his associates [8] on the beneficial effect of high carbohydrate diets on patients with heart failure.

COMMENT

Our results confirm the work of previous investigators in regard to the characteristic manifestations of cardiac impairment caused by insulin hypoglycemia. They further indicate that similar manifestations may be produced in elderly diabetic patients by the therapeutic administration of insulin over longer periods of time. The cardiovascular phenomena accompanying the therapeutic use of insulin are of lesser magnitude than those caused by insulin shock, but they occur at blood sugar levels within the usually accepted normal range. The objective phenomena resulting from insulin therapy, like those caused by insulin hypoglycemia, are accompanied by subjective distress. In both cases the signs and symptoms are abated with the return of higher blood sugar levels.

The electrocardiographic changes following the administration of insulin led us to believe that the heart suffers a depression, which affects conduction in particular. This agrees with the conclusion of Schäffer, Bucka and Friedländer,[5] and is in accord with the well known fact that of all the cardiac properties, conductivity is the most labile. Our conclusions are based on the finding of a decreased amplitude and an increased slurring of the QRS complex, and are further supported by the tendency of the S-T segment and the T wave to shift in a direction opposite to the major initial complex. This is so striking in certain cases as to resemble the changes seen during attacks of angina pectoris, such as reported by Feil and Siegel.[10] In fact, in one of our cases (fig. 2) these changes preceded the attack of angina pectoris.

One of us (L. N. K.[11]), in reviewing the significance of the T wave, has pointed out that the direction of the T wave is determined by two factors: (*a*) the asynchronism of the onset of activity in various fractions of the heart, which, if acting alone, would tend to make the T wave a mirror image of the QRS complex so far as direction is concerned, and (*b*) the unequal duration of activity of the various fractions of the heart. It is the latter factor that is responsible for the T wave being normally in the same direction as the major initial complex. It follows,

10. Feil, H. S., and Siegel, M. L.: Electrocardiographic Changes During Attacks of Angina Pectoris, Am. J. M. Sc. **175**:255, 1928.

11. Katz, L. N.: The Significance of the T Wave in the Electrogram and Electrocardiogram, Physiol. Rev. **8**:447, 1928.

therefore, that any tendency for the T wave to become opposite in direction to the major initial complex can mean (*a*) that the inequality in the duration of activity in the various heart fractions is decreased, (*b*) that the asynchronism of the onset of activity is increased, i. e., conduction is slowed, or (*c*) that both factors operate. In view of the other changes noted in the electrocardiogram, it is more logical to explain the changes on the basis of a delay in conduction. The previous reports that insulin causes inversion of the T wave were probably made because the authors were dealing with upright major initial deflections.

The analysis of the changes in the S-T segment is complicated because there are two possible causes for the shifts in this segment: (*a*) the injury of large regions of the heart, usually due to myocardial ischemia, and (*b*) the beginning of the recovery process in this segment, so that a sharp differentiation between the S-T and the T wave is not always feasible. The fact that during the period that insulin is being administered the S-T segment slopes to meet and fuse with the T wave favors the view that the explanation proposed for the change in the T wave holds, in part at least, for the S-T segments. If, as Ernstene and Altschule [12] have concluded, insulin causes an increase in the minute volume of circulation, and this applies equally to the heart with coronary sclerosis, it is not unlikely that the coronary supply will fail to keep pace with the work of the heart. Myocardial ischemia, with its electrocardiographic and anginal signs, would therefore follow (Katz and Wallace [13] and Feil and Siegel [10]).

The case (Lena S.) in which the deleterious effects of insulin on the heart were reproduced by the use of a low carbohydrate diet alone is of particular significance in elucidating the mechanism by which insulin produces its effects. The fact that no insulin was administered throughout this therapeutic experiment rules out the possibility of ascribing our results to the presence of a toxic component in commerical insulin. An excess of endogenous insulin can hardly be postulated since the patient had diabetes. The experimental impairment of the myocardium in this patient cannot, therefore, be due to either an excess of insulin in the organism or a toxic component of administered commercial insulin. The effects observed must therefore be ascribed to the lack of readily available carbohydrate for the use of the already damaged heart. The relief of the objective manifestations and subjective symptoms of her cardiac distress by the high cabohydrate diet was striking. The hypoglycemic rather than the direct toxic action of insulin is also

12. Ernstene, A. C., and Altschule, M. D.: The Effect of Insulin Hypoglycemia on the Circulation, J. Clin. Investigation **10**:521, 1931.

13. Katz, L. N., and Wallace, A. W.: The Rôle of Cardiac Ischemia in Producing R-T Deviations in the Electrocardiogram, Am. J. M. Sc. **181**:836, 1931.

indicated by the case (Ben. S.) in which the patient received insulin during both experimental periods, but in whom the characteristic phenomena developed only when the insulin was sufficient to cause a considerable reduction in his blood sugar level and glycosuria.

In most of the experiments with insulin the electrocardiographic changes tended to follow the fluctuations in blood sugar. They did not, however, occur at particular blood sugar levels, nor did the extent of the electrocardiographic variations bear any apparent quantitative relation to the total fall in blood sugar. The rapidity of change in the blood sugar level seemed to be an important factor. The lack of quantitative correlation between the different experiments probably depends on the fact that we were dealing with patients whose hearts were damaged in varying degrees. Our results, like those of Smith and his co-workers,[5] show the increased demands of the impaired myocardium for carbohydrate. It is a most interesting observation that the fact that these patients were diabetic—and this applies especially to the patient who received no insulin—did not prevent the increased requirement of the heart for sugar, or the beneficial action of the increased carbohydrate when given.

The deleterious effect of insulin on the myocardium and the antagonistic action of carbohydrate in this regard seem rather surprising in the light of the generally accepted view that insulin facilitates the utilization of dextrose. This situation is not, however, as paradoxical as it appears at first glance. The function of insulin for which there is most experimental proof is its ability to cause the storage of carbohydrate in the tissues of the organism. If it may be supposed (and we have reason to believe that it is so) that the damaged myocardium stores dextrose only with difficulty, then the lowering of the blood sugar by insulin will decrease or remove the heart's source of dextrose supply without at the same time stocking up the myocardium with its carbohydrate needs for the interim. This would be comparable to a rapid lowering of the blood sugar level in a normal animal. The antagonistic actions of insulin and dextrose on the heart are probably, therefore, more apparent than real.

The clinical aspects of our results have been discussed elsewhere (Strouse, Soskin, Katz and Rubinfeld[14]). We do not think that they should be interpreted to mean that insulin in itself is harmful to the elderly diabetic patient with cardiovascular disease. Our work, however, does indicate that whether or not such patients are receiving insulin, the carbohydrate supply to the damaged myocardium is of the greatest importance.

14. Strouse, S.; Soskin, S.; Katz, L. N., and Rubinfeld, S. H.: The Treatment of the Older Diabetic with Cardiovascular Disease, J. A. M. A. **98**:1703 (May 14) 1932.

APPENDIX

The following tables give a description of the electrocardiograms shown in the summary protocols in figures 1, 2, 4 and 5.

TABLE 2.—*Acute Experiment on Harry S. (fig. 1)*

	Before Insulin	After Insulin	After Dextrose
QRS complex	Lead I, upright Leads II and III, inverted Slurred in all leads; duration, 0.12 second	Smaller amplitude in all leads; duration slightly longer	No increase in amplitude; duration decreased
S T interval	Lead I, negative Lead II, iso-electric Lead III, slightly positive, rising	Lead I, more negative Lead II, slightly negative and rising Lead III, more positive	Lead I, unchanged Lead II, more nearly iso-electric Lead III, returns to original configuration
T wave	Lead I, upright Lead II, inverted and small Lead III, inverted and cove-shaped	Lead I, progressively smaller Lead II, becomes upright Lead III, progressively smaller, then becomes upright and progressively larger	Lead I, unchanged Lead II, becomes smaller Lead III, becomes smaller
P wave	Upright in all leads; small in lead III	Slightly broader	No change
P R interval	0.16 second	0.18 second	0.15 second
Rhythm	Nodal extrasystoles	Extrasystoles increased in frequency	Frequency of extrasystoles decreased

TABLE 3.—*Acute Experiment on Lena S. (fig. 2)*

	Before Insulin	After Insulin	After Dextrose
QRS complex	Lead I, upright Lead II, upright and small Lead III, inverted Slurred in all leads	Lead I, larger Lead II, unchanged Lead III, larger	Lead I, temporarily smaller Lead II, unchanged Lead III, temporarily smaller
S T interval	Lead I, negative Lead II, almost iso-electric Lead III, positive	Lead I, more negative Lead II, becomes negative Lead III, more positive	Lead I, temporarily iso-electric Lead II, temporarily positive Lead III, no change
T wave	Lead I, tiny, upright Lead II, small, inverted Lead III, small, inverted	Lead I, slightly larger Lead II, becomes slightly upright Lead III, becomes almost iso-electric	Lead I, temporarily indiscernible Lead II, temporarily larger Lead III, temporarily larger
P wave	Lead I, upright Lead II, small and notched Lead III, inverted	Lead I, taller Lead II, broader and taller Lead III, upright and notched	Lead I, smaller Lead II, narrower Lead III, narrower
P R interval	0.16 second	0.16 second	0.14 second
Rhythm	Sinus rhythm	Paroxysmal auricular fibrillation; ventricular extrasystoles	Temporary sinus tachycardia and later return of auricular fibrillation; extrasystoles disappear

TABLE 4.—*Therapeutic Experiment on Harry S. (fig. 4)*

	Before Insulin	During Insulin
QRS complex	Lead I, upright Leads II and III, inverted Slurred in all leads; duration, 0.12 second	Smaller amplitude in all leads, duration unchanged
S-T interval	Lead I, negative Lead II, iso-electric Lead III, positive	Lead I slightly less negative Lead II, iso-electric Lead III, progressively more positive
T wave	Lead I, upright Lead II, inverted and small Lead III, inverted and cove-shaped	Lead I, progressively smaller Lead II, becomes iso-electric, then progressively more positive Lead III, becomes less negative, then diphasic, then upright
P wave	Upright in all leads	Remains unchanged
P-R interval	0.16 second	Remains unchanged
Rhythm	Slight sinus arrhythmia	Sinus arrhythmia more marked; auricular extrasystoles appear

TABLE 5.—*Therapeutic Experiment on Lena S. (fig. 5)*

	Low Carbohydrate Diet	High Carbohydrate Diet
QRS complex	Lead I, upright Lead II, upright and small Lead III, inverted Slurred in all leads	Lead I, progressively smaller Lead II, slightly smaller Lead III, progressively smaller
S-T interval	Lead I, negative Lead II, slightly negative, rising Lead III, positive, rising	Lead I, less negative Lead II, becomes iso-electric Lead III, less positive
T wave	Lead I, small and positive Lead II, small, progressively more positive Lead III, diphasic	Lead I, no change Lead II, becomes negative and small Lead III, becomes negative
P wave	Lead I, upright Lead II, upright Lead III, diphasic	Lead I, smaller, narrower Lead II, smaller, narrower Lead III, no change
P-R interval	0.16 second	0.16 second
Rhythm	Frequent attacks of paroxysmal auricular fibrillation	No attacks of fibrillation

SUMMARY

1. The characteristic myocardial impairment resulting from insulin hypoglycemia reported by other workers has been confirmed.

2. Our results indicate that the changes in the S-T segment and T wave of the electrocardiogram following the administration of insulin depend on the direction of the major deflection of the QRS complex, a correlation hitherto overlooked.

3. Similar results have been obtained by the therapeutic use of insulin, in amounts that did not cause hypoglycemia, in the treatment of elderly diabetic patients with cardiovascular disease.

4. The results obtained with insulin have also been obtained by the use of a low carbohydrate diet without insulin.

5. The objective manifestations of myocardial impairment obtained with both insulin and a low carbohydrate diet were almost always accompanied by complaints of subjective distress in our patients.

6. The deleterious action of insulin on the heart is probably not due to a direct toxic action on the myocardium, but is probably related to the supply of carbohydrate that is readily available to this organ.

Dr. David C. Cohn, in the Department of Chemistry, made the chemical analyses.

YELLOW ATROPHY OF THE LIVER

REPORT OF A CASE, WITH PARTICULAR REFERENCE TO THE METABOLISM OF COPPER

A. H. GORDON, M.D.
AND
I. M. RABINOWITCH, M.D.
MONTREAL, CANADA

The wide distribution of copper in living materials has been recognized for some time. Elvehjem and Lindow [1] reviewed the older literature with respect to the copper content of plants. The data suggest that copper should be placed in the group of catalytic elements; it is found in greater amounts in more active portions of plants (young shoots, leaves); buds contain more than wood or bark, and its addition to raw peat soil was found to stimulate plant growth. Rose and Bodansky [2] reviewed the older literature with respect to the copper content of animal tissue. With improvement of methods for the detection and quantitative estimation of minute amounts of copper, there is much to support the view that this element is a universal constituent of protoplasm; spectroscopic [3] and chemical [4] analyses indicate its presence in every organ, human and animal. Failure to find it in the past appears to have been due to the limitations of the methods available for its detection when present in minute quantities. Thus, though Palet [5] was unable to find copper in 54 normal human livers, spectroscopic analysis [3] indicates in general, a higher concentration in this organ than in any other organ in the body. The amounts found vary widely. In 160 samples of common food materials, animal and vegetable, the copper content ranged from 0.1 to 44.1 Gm. per kilogram of fresh material.[4b]

From the Medical Service of Dr. A. H. Gordon and the Department of Metabolism, the Montreal General Hospital.

1. Elvehjem, C. A., and Lindow, C. W.: J. Biol. Chem. **81**:435, 1929.

2. Rose, W. C., and Bodansky, M.: J. Biol. Chem. **44**:99, 1920.

3. Sheldon, J. H., and Ramage, H.: Biochem. J. **25**:1608, 1931.

4. (*a*) White, C. P.: Lancet **2**:701 (Oct. 1) 1921. (*b*) Lindow, C. W.; Elvehjem, C. A., and Peterson, W. H.: J. Biol. Chem. **81**:435, 1929; **82**:465, 1929. (*c*) McHargue, J. S.: Am. J. Physiol. **72**:583, 1925. (*d*) Maquenne, L., and Demoussey, E.: Comp. rend. Acad. d. sc. **170**:87, 1920. (*e*) Fox, H. M., and Ramage, H.: Proc. Roy. Soc., London, s. B., **108**:157 (April 20) 1931.

5. Palet, L. P. J., quoted by Bodansky, M.: J. Biol. Chem. **48**:361, 1921.

BIOLOGIC SIGNIFICANCE OF COPPER

In the past it was generally held that the presence of copper in biologic materials was of no physiologic significance. In marine life, it was generally attributed to contamination by sea water, and in man, as late as 1925, it was attributed by Mallory [6] to contamination by food. Mallory concluded that "The reason that copper is so generally found in minute quantities in human organs is not due to its being a normal constituent of the tissues but because man is constantly exposed to taking the metal into his system through foods and drinks contaminated with it." The use of copper as a coloring agent for canned foods, its use as a preventative of growth of algae in water and its use in the manufacture of utensils for distillation of liquors were cited as some of the causes of contamination.[7] Mallory, apparently, overlooked the extensive work of Rose and Bodansky.[2] From the work of Rose and Bodansky, it would appear that copper is an essential constituent of normal tissue and not an accidental finding due to the ingestion of foods contaminated with this element. There is much to support this view. The wide distribution of copper-containing proteins;[8] the importance of copper in the formation of hematocyanine (Fredericq, 1878) and the relationship between hematocyanine and hemoglobin (Henze, 1901); the rôle of copper in the synthesis of hemoglobin in mammals;[9] its presence in fetal organs in greater concentration than in the corresponding organs of the adult;[10] its presence in young and growing plants;[4d] its presence in milk, human and animal,[11] and the absence of a relationship between the copper content and the geographical distribution of corresponding food materials [4b] are some of the conditions which suggest that its presence in biologic material is of fundamental importance.

PATHOLOGIC SIGNIFICANCE OF COPPER

Can excess quantities of copper do harm? Mallory, Parker and Nye [7] first suggested that hemochromatosis was due to chronic copper poisoning. Chronic poisoning with the salts of copper produced in rabbit livers changes comparable in many ways with those found in

6. Mallory, F. B.: Am. J. Path. **1**:117, 1925.

7. Mallory, F. B.; Parker, F., Jr., and Nye, R. N.: J. M. Research **42**:461, 1921.

8. Severy, H. W.: J. Biol. Chem. **55**:79, 1932. Vickery, H. B., and Osborne, T. B.: Physiol. Rev. **8**:393, 1928.

9. Waddell, J.; Steenbock, H.; Elvehjem, C. A., and Hart, E. B.: J. Biol. Chem. **77**:777, 1928; **83**:251, 1925. Titus, R. W.; Cave, H. W., and Hughes, J. S.: ibid. **80**:565, 1928.

10. Bodansky, M.: J. Biol. Chem. **48**:361, 1921. Sheldon and Ramage.[3]

11. Supplee, G. C., and Bellis, B.: J. Dairy Sc. **5**:455, 1922. Hess, A. F.; Supplee, G. C., and Bellis, B.: J. Biol. Chem. **57**:725, 1923.

hemochromatosis in man. From a study of clinical records, Mills,[12] while working with Mallory, concluded that chronic poisoning with copper may be the cause of hemochromatosis. Particular attention was paid in this study to the possibility of exposure of the patients to copper. Analysis of the data, however, shows that though they are suggestive, they are not convincing; nor are Mallory's chemical data convincing. Six livers were analyzed with respect to their copper contents. In the first two organs examined (A22.64; A22.67) no copper was found, but the statement is made that "examinations were made by a cruder method which would not show minute amounts." The data obtained in the remaining cases were not unlike those found in four "control" cases. No mention is made of the chemical methods employed. As will presently be shown in the report of our case, this is an important consideration in the interpretation of results. The absence of a causal relationship between hemochromatosis and chronic copper poisoning is suggested from experiences with Koreans. The latter, as R. G. Mills pointed out,[13] numbering about 17,000,000, are continually exposed to copper; brass is the universal material out of which they manufacture the rice and other food bowls, spoons, etc. Brass is also used for wine bottles and some of the stills for making fermented liquors. Food not only is carried in brass vessels, but also is cooked in them and kept in them from meal to meal. The nature of some of the foods is such that they would exert a solvent action on the metal. The ingestion of copper begins shortly after birth and continues until death. In spite of this, Mills was unable to find any disturbance of pigmentation in 100 autopsies. Diabetes, a condition commonly associated with hemochromatosis, is also rare among these natives; the incidence found was about 0.1 per cent among hospital records. These observations fit with those of Flinn and von Glahn,[14] who were unable to confirm Mallory's experimental findings; copper and its compounds did not cause the deposition of pigment in the livers of rabbits or other animals used, and the feeding of a diet of carrots exclusively caused deposition of a pigment in the livers of rabbits in every way identical with that ascribed to copper.

Limited significance is apparently attached to copper as an industrial poison among workers in the United States.[15] The ill health found among copper miners or workers with the metal is largely attributed

12. Mills, E. S.: Hemochromatosis with Special Reference to Its Frequence and to Its Occurrence in Women, Arch. Int. Med. **34**:292 (Sept.) 1924.

13. Mills, R. G.: The Possible Relation of Copper to Disease Among the Korean People, J. A. M. A. **84**:1326 (May 2) 1925.

14. Flinn, F. B., and von Glahn, W. C.: J. Exper. Med. **49**:5, 1929.

15. Hamilton, A.: Industrial Poisons in the United States, New York, The Macmillan Company, 1925.

to other environmental conditions (heat, overexertion, irritating dust and the presence of lead or arsenic). Brass poisoning, brass founder's ague, is, according to the consensus, caused by the zinc in the alloy and not by the copper.

In spite of the conflicting data, there is reason to believe that excess quantities of copper may be harmful. It is rather difficult to reconcile the aforementioned views of workers in industrial poisoning with the "brassy" taste, the green line on the gums and the green discoloration of the sweat frequently found among workers in copper mines; nor are the views held by American authorities generally accepted. Until recently, the amount of copper allowed in foods in England was limited to 2 grains (0.13 Gm.), copper sulphate, hydrous ($CuSO_4.5H_2O$) a pound. Under the new (1925) regulations, the addition of copper salts is entirely prohibited.[16] It is of interest to note that though no hemochromatosis was found among the Koreans, cirrhosis of the liver is common and is found frequently in young persons below the age of

TABLE 1.—*Results of Analyses in Twenty-Two Cases*

	Cirrhosis			No Cirrhosis		
Number of cases	13			9		
	Maximum	Minimum	Average	Maximum	Minimum	Average
Milligrams of copper per kilograms of fresh material	85.6	2.9	20.8	9.9	0.6	5.4
Total milligrams of copper per organ	117.0	3.31	35.5	21.39	0.72	11.3

15 years. R. G. Mills suspects that this is due to chronic copper poisoning. The data of Cherbuliez and Ansbacher[17] are of interest here. These authors recorded analyses of the livers of 9 patients without, and of 13 patients with, cirrhosis. In each case are recorded the weight of the liver and the milligrams of copper per kilogram of fresh material. From these data, it is obviously possible to determine the maximum, minimum and average values and to calculate the total amounts of copper found in the different organs. Table 1 gives a summary of these calculations.

The foregoing finding of more copper in the liver in cirrhosis than in the control cases is not an isolated experience and suggests an etiologic relationship between copper and this condition of the liver. Unfortunately, exact comparisons of the different values obtained by different observers are not possible, because of the different values recorded. For example, some authors record milligrams of copper per kilograms of dry tissue, but fail to record the water contents of the organs; others

16. Cox, H. E.: Chemical Analysis of Foods, London, J. & A. Churchill, 1926.

17. Cherbuliez, E., and Ansbacher, S.: Arch. f. klin. Med. **278**:365, 1930.

record milligrams of copper per kilograms of fresh tissue and fail to state the total weight of the organs. Approximate comparisons, however, may be made in many cases when the total weights of organs are given, by assuming that the liver contains approximately 75 per cent of water. This value is in accordance with recorded analyses[18] and with our own. With the foregoing assumption, there is remarkable uniformity with respect to the average copper contents of "normal" livers. The observations have, therefore, prompted the report of the following case.

REPORT OF CASE

History.—A deeply jaundiced man, aged 48, a laborer, was admitted to the medical service of one of us (A. H. G.) on May 25, 1932, in a semicomatose state, with the following history: During the last fifteen years he had apparently suffered from some gastro-intestinal condition, consisting of eructations of gas that came on about one and one-half hours after meals and occasional vomiting. During the last year, he complained of pain in the epigastric region, which came on about one-half hour after each meal and was relieved by bismuth preparations. The jaundice gradually increased in intensity and dated from about five weeks prior to admission; however, there was also a history of occasional slight attacks during the last fifteen years. He had lost about 1 pound (0.5 Kg.) a day since the onset of the jaundice, but had continued to work until five days before admission, when he became drowsy. Clay-colored stools were frequently noted. The history was otherwise irrelevant, except that he had worked in a copper mine about fifteen years previously, and his illness apparently dated from that period.

The family history was irrelevant.

Examination.—On admission, the physical findings were essentially negative, except for the jaundice, fluid in the peritoneal cavity and a definitely diminished area of dulness of the liver.

The laboratory findings were as follows: Two urinalyses were made. The specific gravities were 1.012 and 1.010, respectively, and at both examinations, large amounts of albumin, bile and bile-stained casts were found. There were also a few pus cells.

The contents of the stomach showed occult blood and an absence of free hydrochloric acid.

The stools were clay-colored and contained no blood.

The blood findings were as follows: red cells, 4,250,000; white cells, 5,700; hemoglobin, 85 per cent; smear, normal, and Wassermann reaction, negative.

On May 26, chemical analysis showed: urea nitrogen, 22 mg. per hundred cubic centimeters; creatinine, 1.5 mg.; amino-acid, 7.5 mg.; sugar, 0.169 per cent (not fasting); van den Bergh, 11.2 mg. of bilirubin per hundred cubic centimeters of blood (28 units).

On May 30, chemical analysis showed: urea nitrogen, 35 mg. per hundred cubic centimeters; creatinine, 2 mg.; sugar, 0.147 per cent; van den Bergh, 13.6 mg. of bilirubin per hundred cubic centimeters of blood (34 units). Examination showed a trace of urobilinogen.

---

18. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

The following clinical note was made by one of us (A. H. G.) on May 27:

"The picture is that of yellow atrophy, but the duration of the illness is rather long. The absence of an alcoholic history and absence of engorgement of the abdominal and facial veins are strongly against the classical Laennec cirrhosis. A form of liver atrophy going on to fibrosis—so-called toxic or infectious type of hepatic cirrhosis—more nearly fits the case."

Course.—From the time of admission of the patient to the hospital, there was a downward progress; he became rapidly comatose, and food was confined to intravenous injections of dextrose. The temperature tended to be subnormal, ranging from 96.4 to 98 F., with an average of 97 F. The patient died on June 2, eight days after admission.

Autopsy.—An autopsy was performed eight hours after death, and the postmortem diagnosis was yellow atrophy of the liver; exudative cholangeitis with marked bile stasis.

As soon as the liver was removed from the body, it was weighed and examined grossly. A portion was removed for examination by the pathologist, and the remainder was sent to the metabolism laboratories for chemical analyses.

Report of Pathologist (Dr. L. J. Rhea): The liver showed a marked and uniform reduction in size, weighing only 680 Gm. It was flabby in consistency. The capsule was wrinkled, especially near the thin, sharp, anterior border. The general color of the liver tissue was reddish yellow. Scattered throughout the liver were rather widely separated, rounded and definitely circumscribed yellow nodules. These scattered nodules projected as small eminences on the surface beneath the capsule, but, being widely separated and relatively few in number, the greater part of the surface of the liver was free from nodules. The architectural markings as seen on the cut surface were suggestive of a general collapse resulting from widespread destruction of the glandular tissue of the liver. The nodules were interpreted as areas of regeneration of the liver tissue.

Microscopic examination of sections taken from various parts of both lobes of the liver showed the general architecture to be markedly disturbed. Little traces of the normal lobular structure remained. All sections showed widespread areas of complete or almost complete necrosis, areas of fibrosis with bile duct proliferation and hyperplastic nodules of regenerated liver tissue. The increase in fibrous tissue was partly an apparent increase due to destruction of the glandular tissue with collapse of the lobule, but there was also a true increase in fibrous tissue. There was evidence of a widespread cholangeitis. The fibrous bands, in which the proliferating bile ducts lay, were densely infiltrated by large numbers of lymphocytes and smaller numbers of polymorphonuclear neutrophils. The lumens of many of the bile ducts contained "pus cells." The occurrence of marked retention of bile, apparently resulting from the cholangeitis, was indicated by the presence of yellow bile pigment lying free in the areas of necrosis, within macrophages in the fibrous bands, in the epithelial cells and lumens of the bile ducts and in the polygonal cells and distended bile canaliculi of still intact liver cords. In many places traces of the original lobular structure were to be seen in the form of small, collapsed, completely necrotic lobules outlined by fibrous bands containing proliferating bile ducts. Otherwise, there was no evidence of the normal lobular structure. Frozen sections stained with scharlach R did not show any excessive deposition of fat in the liver.

Chemical Analyses: A portion of the liver was minced, weighed and dried to a *constant* weight, in order to determine the water and solid contents. A portion

of the dried material was used for an estimation of the fat content. The results were as follows:

Weight	680 Gm.
Water content	84.3 per cent
Total solids	15.7 per cent
Fat (Soxhlet extraction)	2.6 per cent
Fat-free solids	13.1 per cent

It will be observed that, compared with the normal liver, the water content was increased, but the fat content was within the normal limits. The liver, therefore, differed from that generally found in chloroform and phosphorus poisoning and fatty degeneration in general, in which the fat content may represent as much as 25 per cent or more of the total weight of the organ.

Copper Analyses: A brief reference is here necessary to copper analyses in general, since, as stated before, the interpretation of the data depends largely on the technic employed.

Within recent years, because of the general recognition of the possible physiologic rôle of copper, chemists have been obliged to find more sensitive methods, for both the detection and the quantitative estimation of minute amounts of this metal. A number of methods have been developed, each of which is quantitative, providing due consideration is given to the various technical details, and selection of the method from those available is based on the amounts of copper in the material, as follows:

Method	Amount of Copper (Mg.)
1. Chromotropic	0.002-0.10
2. Carbamate	0.010-0.050
3. Rhodanine-pyridine	0.050-0.100
4. Xanthate	0.100-0.200

It will be observed that as little as 0.002 mg. can be measured. As little as 0.1 mg. can be estimated with a high degree of accuracy. A variety of precautions is necessary for quantitative work.

The foregoing procedures apply to copper in inorganic form and in simple solution. Regardless of the method, therefore, a preliminary necessary procedure is the destruction of organic material. The two chief dangers at this stage are loss of copper or the addition by contamination. The necessary precautions have been dealt with elsewhere.[19] Of the two methods available, dry and wet digestion, the latter, at least in our experience, is preferable. Suitable dilution of the clear solution obtained after oxidation of the organic material, prior to the application of the different methods, makes possible the use of all the aforementioned methods. It is our practice to use the average value obtained from 3 methods. In the analysis of the liver in this case, the following results were obtained:

Method	Mg. of Copper per Kilogram of Fresh Material
Xanthate	185.3
Carbamate	178.6
Rhodanine-pyridine	174.2
Average	179.3

19. Ansbacher, S.; Remington, R. E., and Culp, F. B.: J. Indust. & Engin. Chem. **3**:314, 1931.

As far as could be ascertained from the literature, the amount found in this case per unit weight and fresh material is the largest on record. Because of this finding, 4 other organs obtained from autopsies were examined. The amounts found were well below those found in this case of yellow atrophy (table 2).

In view of the intimate association between copper and arsenic in metals in general and in view of the well recognized causal relationship between arsenic and liver degeneration, it was considered advisable to analyze the liver in this case with respect to arsenic. The procedure used was standard and conformed in all details to our routine in toxicologic analysis; the organic matter was destroyed by the Fresenius-von Babo method; the mixture was then diluted with hot water, treated with dilute sulphuric acid and filtrated. The clear filtrate was heated to expel excess hydrochloric acid and treated with arsenic-free hydrogen sulphide. The precipitate obtained with the latter (not necessarily arsenic) was extracted with ammonia and yellow ammonium sulphide, and the filtrate was tested for

TABLE 2.—*Results of Analyses in Four Autopsy Specimens*

Autopsy No.	Diagnosis	Weight of Liver, Gm.	Mg. of Copper per Kg. of Fresh Material
A-32-131	Carcinoma of the lung	1,650	11.2
A-32-133	General pyogenic infection, probably of pelvic origin	3,320	1.9
A-32-135	Tuberculosis	1,600	26.4
A-32-156	Tetanus	1,770	2.3
	Average		10.4

arsenic by the Marsh technic. No arsenic was found. In order to determine whether extremely minute amounts of arsenic might be present, the Gutzeit colorimetric method was used.[20] No arsenic was found.

RÉSUMÉ

The literature on the metabolism of copper is briefly reviewed, and though the data are not conclusive, they do suggest that copper, a normal constituent of food, may be harmful when administered in excess quantities.

A case of acute yellow atrophy of the liver is reported in which the liver was found to contain an enormous amount of copper. In spite of the large amount of copper, there was no arsenic. Though it may be difficult to associate the anatomic findings in the liver with the exposure of the patient to copper as long as fifteen years ago, there is a reasonable chemical basis for this association. There is, first, the incontestable fact that the liver contained a large amount of copper—as far as we could ascertain, the largest amount on record. It is suggested that the failure of the liver to excrete the copper may have been due to the fact

20. Scott, W. W.: Standard Methods of Chemical Analysis, New York, D. Van Nostrand Company, Inc., 1927.

that copper forms with protein a series of quite stable proteinates. (The blue copper-containing protein of octopus blood, hematocyanine, is an example.) The liver is also rich in products of protein digestion, many of which also form with copper quite stable compounds. This fact is frequently made use of in quantitative analysis. For example, the relative insolubility of the compound formed by copper and aspartic acid serves commonly for the estimation of this acid.

The purpose of reporting our case is to prompt further investigation, in view of the present widespread and increasing use of copper therapeutically. Though copper may have its use, its too general use might do harm. An analogy is suggested in the experiences with the incorporation of iodine in table salt for the prevention of goiter.

DISTENTION AS A FACTOR IN INTESTINAL OBSTRUCTION

RAYMOND C. HERRIN, PH.D.
AND
WALTER J. MEEK, PH.D.
MADISON, WIS.

The voluminous literature on intestinal obstruction has been adequately reviewed by Cooper [1] and Ochsner.[2] Although a toxemia is still generally regarded as the cause of all symptoms, a small group has dissented from this view and presented experimental evidence to show that death from high intestinal obstruction is probably due to nontoxic factors such as dehydration, decrease in blood volume, loss of electrolytes, loss of something specific in the gastro-intestinal secretions or alkalosis. The evidence for this point of view rests among others, principally on the work of Hartwell and Houget,[3] White and Bridge,[4] Burgess, Walsh and Ivy,[5] Jenkins,[6] White and Fender,[7] Armour and his co-workers [8] and Elman and Hartman,[9] all of whom have shown pro-

From the Department of Physiology, University of Wisconsin School of Medicine.

Made possible in part by a grant from the Wisconsin Alumni Research Foundation.

1. Cooper, H. S. F.: The Cause of Death in High Obstruction, Arch. Surg. **17**:918 (Dec.) 1928.

2. Ochsner, A.: Acute Intestinal Obstruction, Surg., Gynec. & Obst. **52**:702, 1931.

3. Hartwell, J. A., and Houget, J. P.: Experimental Intestinal Obstruction in Dogs with Especial Reference to the Cause of Death and the Treatment by Large Amounts of Normal Saline Solution, J. A. M. A. **59**:82 (July 13) 1912.

4. White, J. C., and Bridge, E. M.: Loss of Chloride and Water from the Tissues and Blood in Acute High Intestinal Obstruction, Boston M. & S. J. **196**: 196, 1927.

5. Burgess, J. P.; Walsh, E. L., and Ivy, A. C.: Prolongation of Life of Dogs with Experimental Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **25**:105, 1927.

6. Jenkins, H. P.: Prolonging Life in High Obstruction by Administration of Salt Solutions Below Point of Obstruction, Proc. Soc. Exper. Biol. & Med. **28**: 111, 1930.

7. White, J. C., and Fender, J. A.: The Cause of Death in Uncomplicated High Intestinal Obstruction, Arch. Surg. **20**:897 (June) 1930.

8. Armour, J. C.; Brown, T. G.; Dunlop, D. M.; Mitchell, T. C.; Searls, H. H., and Stewart, C. P.: Studies on High Intestinal Obstruction, Brit. J. Surg. **18**:467, 1931.

9. Elman, R., and Hartman, A. F.: Experimental Obstruction of the Terminal Duodenum and Ileum, Surg., Gynec. & Obst. **53**:307, 1931.

longation of life by restoration of the salt and water volume in animals with experimental obstruction. White and Bridge have found that the loss of chloride in the blood parallels a loss in the tissues. Survival brought about by reinjection of vomited secretions (Jenkins, White and Fender) or by relieving the obstruction with retention of the intestinal contents (Raine and Perry)[10] is, of course, opposed to the idea of toxemia. The work of Dragstedt and his co-workers[11] on loss of the digestive fluids also supports this point of view. None of these investigators deny the possibility of a toxemia in case the obstruction is complicated by strangulation, necrosis or peritonitis.

In actual obstruction, or in its counterpart by closed intestinal loops, the hydrostatic pressure of the accumulating fluids brings about considerable distention. This important factor, the subject of the present research, has received attention from relatively few investigators. Van Zwalenburg[12] showed that intra-intestinal pressures of 90 mm. of mercury delayed the flow in all the blood vessels, but that it took a pressure of 130 mm. to stop the circulation. Dragstedt, Lang and Millet[13] found that the order of sensitiveness to intra-enteric pressure was duodenum, jejunum and ileum, and that a pressure of 80 mm. of mercury reduced the jejunal blood flow to around 60 per cent. Sweet, Peet and Hendrix[14] looked on this distention and consequent rupture as the cause of death. Dragstedt, Dragstedt, McClintock and Chase[15] believed that distention made the intestinal wall permeable to the toxins found in the lumen as the result of bacterial action on proteins or their split products. In later papers, Dragstedt[16] attributed the toxemia and decrease in blood chlorides to the distention of the closed segments. The mechanism suggested was the powerful secretogogue action of the toxic fractions accompanied with a failure of reabsorption.

---

10. Raine, F., and Perry, M. C.: Intestinal Obstruction, Arch. Surg. **19**:478 (Sept.) 1929.

11. Dragstedt, L. R.; Montgomery, M. L.; Matthews, W. B., and Ellis, J. C.: Fatal Effect of the Total Loss of Gastric Juice, Proc. Soc. Exper. Biol. & Med. **28**:110, 1930. Dragstedt, L. R., and Ellis, J. C.: The Fatal Effect of the Total Loss of Gastric Juice, Am. J. Physiol. **93**:407, 1930.

12. Van Zwalenburg, C. V.: Strangulation Resulting from Distention of Hollow Viscera, Ann. Surg. **46**:780, 1907.

13. Dragstedt, L. R.; Lang, V. F., and Millet, R. F.: The Relative Effects of Distention on Different Portions of the Intestine, Arch. Surg. **18**:2257 (June) 1929.

14. Sweet, J. E.; Peet, M. M., and Hendrix, B. N.: High Intestinal Stasis, Ann. Surg. **63**:720, 1916.

15. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction: II. A Study of the Factors Involved in the Production and Absorption of Toxic Materials from the Intestine, J. Exper. Med. **30**:109, 1919.

16. Dragstedt, L. R.: Blood Chemistry in Intestinal Obstruction, Proc. Soc. Exper. Biol. & Med. **25**:239, 1928. Dragstedt, Lang and Millet.[13]

Raine and Perry,[10] working on rabbits, believed that distention increased intestinal peristalsis and secretion and diminished reabsorption. Although they did not exclude toxemia, they attributed most of the symptoms to a loss of sodium chloride. Recently Burget,[17] has attached closed intestinal loops to the anterior body wall where they can be reached by the hypodermic needle. If the pressure is kept down the animals survive, but if distention is allowed to occur, there is vomiting, refusal of food, rupture of the loop and death from peritonitis. The changes in the chemical composition of the blood are relatively unimportant.

The purpose of the present investigation has been to find the cause of the symptoms and fatal outcome which follow a known distention of the intestine when uncomplicated by strangulation, rupture, necrosis or peritonitis.

EXPERIMENTAL PROCEDURES

With surgical asepsis, Thiry, Thiry-Vella and modified Thiry fistulas were made in dogs, the continuity of the intestine being reestablished by lateral anastomosis. In the modified type the intra-abdominal end of the fistulous loop was left attached to the upper portion of the jejunum, thus allowing the secretion of the loop to return to the main intestinal tract. All of these loops were taken just below the ligament of Treitz, which at autopsy proved to be about 40 cm. from the pylorus. The loops ranged in length from 15 to 30 cm. In some cases biopsy samples of skin, muscle and intestine were taken for chloride and water analyses. The dogs were not used for the distention experiments until the wound was completely healed, the appetite good and the general condition thrifty. Throughout the experiment the dogs were allowed milk and biscuits ad libitum.

The fistulous loops were distended by inserting a balloon which was fastened to a suitably bent glass tube. The distention began about 4 cm. from the external opening and extended for about 12 to 14 cm. The balloons were inflated with an air pressure of from 75 to 80 mm. of mercury. This pressure was applied daily and in some cases oftener. Between times the pressure gradually fell, but it was not allowed to go below 50 mm. before the next application. In the case of the Thiry fistulas, a small catheter was fastened along the side of the balloon to permit the secretions to escape.

All of the blood examinations were made before the distention experiment began and repeated again at the end. Blood for hemoglobin, erythrocyte and leukocyte estimations was drawn from the marginal vein of the ear after causing a good circulation by rubbing. Blood for alkali reserve, total chloride, nonprotein nitrogen and plasma chloride determinations was drawn from the femoral artery. Blood volume determinations were made according to the Whipple method as outlined by Rowntree, Brown and Roth.[18] Blood was drawn, and brilliant vital

17. (a) Burget, G. E.; Martzloff, K.; Suckow, G., and Thornton, R. C. B.: The Closed Intestinal Loop: I. Relation of Intraloop (Jejunum) Pressure to the Clinical Condition of the Animal, Arch. Surg. **21**:829 (Nov.) 1930. (b) Burget, G. E.; Martzloff, K.; Thornton, R. C. B., and Suckow, G. R.: The Closed Intestinal Loop: II. Observations on Dogs with Jejunal and Ileal Loops and Chemical Analyses of the Blood, Arch. Int. Med. **47**:593 (April) 1931.

18. Rowntree, L. G.; Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Heath and Disease, Philadelphia, W. B. Saunders Company, 1929.

red was injected by way of the internal jugular veins. Hemoglobin was determined by the Newcomer method, blood or plasma chloride by Whitehorn's method, tissue chloride by Van Slyke's method, nonprotein nitrogen by the micro-Kjeldahl method on the blood filtrate and the alkali reserve by the usual Van Slyke and Cullen procedure.

These methods for studying the distention factor of obstruction, we believe, offer advantages over those used by other investigators. The surgical procedures are separated from the experimental. There is no accumulation of intestinal contents, either secretions or food residues. There is no interference with the digestive functions of the rest of the alimentary tract. There is no accumulation of fluid in the distended loop since its contents may either drain exteriorly or back to the normal intestine, according to the type of fistulas. The distending pressure can be regulated. The secretions may be collected and their rate of formation and nature be determined. Through the modified loop, injections may be made into the normal alimentary canal. The experiments can be terminated at any stage of the clinical picture, and they may be repeated on the same animal.

SYMPTOMS AND BLOOD CHANGES SIMILAR TO ACUTE INTESTINAL OBSTRUCTION PRODUCED BY DISTENTION

If distention is a fundamental etiologic factor in acute obstruction, it is necessary to show that experimental distention gives the same general clinical and blood picture as obstruction itself. To settle this point we have performed twenty-five experiments on fifteen dogs with Thiry fistulas and eight experiments on seven dogs with Thiry-Vella fistulas. The two groups responded in exactly the same manner to distention and need not here be further separated from each other. Of the twenty-two dogs, fourteen were allowed to run a fatal course, the average length of life being eight days. The earliest death occurred on the fifth day and only one lived beyond ten days, dying on the fourteenth. After inflation there is soon depression of activity, in some cases retching or vomiting, and by the fourth day, on the average, entire disappearance of appetite. As distention continues, the dog shows loss of weight with signs of emaciation. The coat looses its gloss and the skin becomes dry and inelastic. The muzzle becomes dry and warm, the eyes shrunken and the pulse rapid. Fibrillary tremors and weakness appear in the limbs, and the reflexes are depressed. The temperature decreases one or two degrees, and a leukopenia may be found. The animal shows no sign of pain but gradually passes into coma followed by death.

The blood changes in the foregoing animals are shown in table 1. For the sake of brevity, five are given in detail and averages for the remainder. The results are of interest in showing the widespread effects following increased hydrostatic pressure in an isolated loop. The blood changes that have received most attention in intestinal obstruction are the fall in chloride, the rise in nonprotein nitrogen and the increased carbon dioxide content. In our experiment the blood never failed to

show a decrease in chloride. This drop in blood chloride is not due to a decrease in per cent of plasma, because the chloride concentration of plasma is also reduced. This shows that there is an actual loss of chloride, just as in complete obstruction. The nonprotein nitrogen rose in all cases, the increase being most marked toward the end of the animal's life. The carbon dioxide-combining power in distended loops does not change greatly. An increase is usually found in those animals which show more or less vomiting and a slight decrease in some of the others, which is probably related to the ketosis from reduced food intake. In addition to these three cardinal symptoms, previous workers have generally believed there was dehydration, as evidenced by hemoglobin

TABLE 1.—*Blood Changes in Animals with Distention of Thiry or Thiry-Vella Loops*

			Blood							Plasma		
Experiment No.	Procedure	Weight, Kg.	Hemoglobin, Gm.	Red Blood Cells, Millions	Volume, Cc.	Volume in per Cent of Weight	NaCl, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Alkali Reserve, Cc.	Volume, Cc.	NaCl, Mg. per 100 Cc.	Plasma, per Cent
43	Normal	18.82	13.0	6.85	2,174	11.5	429	34.2	45.7	1,175	627	53.2
	Distention	14.02	17.0	10.06	1,441	9.8	379	39.3	40.5	585	561	40.6
51	Normal	11.30	10.5	5.75	1,186	10.5	495	29.1	40.0	676	610	57.0
	Distention	10.25	14.0	7.25	846	8.2	445	40.0	39.0	495	577	58.5
46	Normal	16.36	12.3	7.59	1,437	8.7	478	30.6	42.8	828	618	57.7
	Distention	13.20	14.2	9.49	1,266	9.6	396	42.9	51.3	740	705	55.7
50	Normal	13.50	14.0	9.67	1,122	9.3	462	29.5	46.4	621	610	55.3
	Distention	11.34	14.5	12.23	911	8.0	330	98.5	52.3	406	495	44.6
40	Normal	12.10	13.8	8.37	1,217	10.0	429	33.8	51.6	306	594	40.0
	Distention	9.88	19.0	10.09	910	9.2	297	70.5	49.0	325	465	35.7
Average changes in per cent		−15	+30	+33	−19		−24	+100	+11	−24	−17	−16
Number of experiments		15	16	13	11		21	21	12	11	5	10

determinations and hematocrit readings. Our animals have shown hemoglobin concentration, an increased red cell count and a decreased plasma percentage. In addition, by direct determinations of blood volume we have invariably found a quantitative decrease in plasma volume. The total blood volume also decreased from 12 to 34 per cent, with two exceptions in which it remained approximately normal.

In dogs with distended loops the total excretion of urea as well as total nonprotein nitrogen in the urine increases until near the end, while the excretion of chloride steadily falls. The quantity of urine remains more or less normal since the water consumed is absorbed by the intact gastro-intestinal tract.

In view of the fact that the symptoms and blood changes just described in our distention experiments are so much like those reported by all workers on acute intestinal obstruction, we believe we are justi-

fied in assuming that the fundamental causes of the two conditions must be much the same. As further evidence, we have repeated our studies on three dogs with surgical obstruction made at the same level from which our loops were taken. The course in these dogs was exactly the same as that in our animals subjected to distention. The blood changes may be seen in table 2.

CAUSE OF DEATH FROM DISTENTION OF INTESTINAL LOOPS AND HIGH OBSTRUCTION

Toxemia.—The idea that toxemia due either to bacterial or autolytic products was the cause of death in obstruction has been generally accepted because the clinical picture resembled that of known toxemias and because even recent experimentation has not given entirely clear-

TABLE 2.—*Blood Changes in Complete Intestinal Obstruction*

			Blood							Plasma		
Experiment No.	Procedure	Weight, Kg.	Hemoglobin, Gm.	Red Blood Cells, Millions	Volume, Cc.	Volume in per Cent of Weight	NaCl, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Alkali Reserve, Cc.	Volume, Cc.	NaCl, Mg. per 100 Cc.	Plasma, per Cent
34	Normal	17.2	15.2	6.83	.....	....	495	31.2	41.3	...	....	51.6
	Obstruction	14.7	17.4	7.25	.....	....	297	187.5	47.3	...	...	50.3
59	Normal	18.0	14.5	9.10	1,759	9.8	445	27.2	40.0	802	594	45.6
	Obstruction	16.7	17.5	10.27	1,529	9.1	247	99.9	49.0	575	495	37.6
61	Normal	12.5	13.7	8.01	1,129	9.0	462	28.5	47.4	545	610	48.3
	Obstruction	11.0	15.0	8.70	910	8.2	313	51.9	51.3	488	429	53.6

cut evidence to the contrary. The relief of symptoms by injections of saline, reintroduction of vomitus below the obstruction, removal of the obstruction with the passage of the intestinal contents, or aspiration of a closed loop, convincing as these procedures at first seem, might all be explained by dilution, neutralization or withdrawal of a hypothetic toxin.

There are three features of our experiments which seem to exclude any possibility of a toxemia. The first of these was drainage of the loops. Mention has already been made that in distending the Thiry fistulas a tube was placed at the side of the balloon which allowed the secretions to flow to the exterior. Compared to the usual obstructions there was thus little material allowed to accumulate for bacterial action. To avoid the criticism that even a small amount of secretion at the bottom of the loop had putrefied and formed toxic products, the Thiry-Vella fistula was introduced, which allowed for drainage at the open end. Although this preparation excluded the possibility of any measurable retention of fluid whatever, the animals still succumbed.

To meet the objection that the death of these animals was really due to the formation of a very potent toxin in minute amounts, a second feature was introduced, namely, a modification of the Thiry fistula by leaving its distal end attached to the continuous intestinal tract. In these experiments, there was no loss of secretion to the outside. Any toxin, however, either bacterial or autolytic, should have been formed and absorbed as before, either in the distended area or in the region below, and death should have resulted even more promptly. These animals, however, proved entirely resistant. Three such animals, after enduring distention for sixteen, seventeen and nineteen days, respectively, remained in normal health and showed no significant blood changes. In one of these animals distention was performed a second time with similar results.

That these animals were not spared because of toxin neutralization in the parts below the loop, a criticism we have already made on previous work, was made evident by a third type of experiment, to be described more fully later, in which the Thiry fistula loop was denervated. Such denervated animals also proved resistant to distention, living indefinitely without any of the symptoms characteristic of obstruction or distention, yet if distended loops produced toxins it should have certainly occurred and the animals should have succumbed. Not only do these experiments seem to us to rule out the idea of a bacterial or autolytic toxemia in intestinal obstruction, but they also dispose of the theory that the intoxication might be due to the absorption of perverted or nondetoxified digestive secretions. Since the secretions of the stomach, pancreas, liver and Brunner's glands follow their normal course and yet the alleged toxic symptoms still appear on distention of unmodified Thiry and Thiry-Vella loops, there must be other causal factors. That there has been no perversion of the intestinal secretion in the loops themselves is shown by the two types of experiments mentioned in which toxic symptoms do not appear.

Autopsy was carefully performed on all dogs that died or were killed at the end of an experiment and in many cases the loop was examined histologically. If the loop showed rupture or there was any peritonitis, the results were discarded. Grossly, the distended segments showed loss of tonus, thinning of the walls, a deeper color than adjoining regions and occasionally some mucosal desquamation in small areas. Histologically, there was marked lymphocytic infiltration, hyperemia with some hemorrhage, and the thining was seen to be due to loss of villi and mucossal glands. These anatomic changes did not seem sufficiently marked to suggest any form of toxemia from tissue breakdown, particularly since they were found both in animals that died as well as

those that survived. Elman and Hartman [9] have described much the same changes in the intestinal wall above the obstructions.

Being unable to find any evidence in support of the various theories of toxemia as a cause of the symptoms and death in distention and obstruction, we turned our attention to nontoxic factors.

Dechlorination, the Essential Change Following Distention.—The chief blood changes which have interested previous observers and to which a number have attributed all the signs and symptoms of obstruction are alkalosis, increased nonprotein nitrogen, dehydration and dechlorination. Our next problem was to find which of these, if any, were responsible for the outcome in our own experiments duplicating high obstruction.

Although the literature on obstruction generally emphasizes marked alkalosis as one of the cardinal symptoms, an inspection of the data presented does not entirely justify that conclusion. Hayden and Orr [19] and Häbler [20] all cite numerous experiments in which carbon dioxide-combining power showed great variabilty, often falling below normal. The high values reported by Hastings, Murray and Murray [21] and Armour [8] and his co-workers seem exceptional, at least for jejunal obstructions.

Alkalosis in itself did not seem related to the fatal outcome in our animals. In twelve dogs the carbon dioxide-combining power of the arterial plasma averaged only 11 per cent higher than normal, the variations being about the same as those reported by many other workers. Furthermore, a number of our animals showed either no change in carbon dioxide-combining power or an actual decrease, and yet they died in the usual manner with the blood changes typical in all other details. Variability in our animals has a rather obvious explanation. Vomiting is a contant symptom of clinical obstruction, and the loss of hydrochloric acid in the vomitus makes for alkalosis. Distention of a short loop may or may not produce vomiting, and it is apt to be moderate if it occurs. Our animals that did vomit were among those that showed increases in alkali reserve.

Increased nonprotein nitrogen invariably occurred in all of our unmodified distention experiments. The amount was often more than doubled, as may be seen in experiment 50, table 1. The lower figures are for samples of blood taken some time before death. Urea itself in

19. Hayden, R., and Orr, T. G.: Experimental Obstruction of the Jejunum, J. Exper. Med. **41**:707, 1921.

20. Haebler, C.: Untersuchungen zur Molekularpathologie des experimentellen Dünndarmverschlusser, Ztschr. f. d. ges. exper. Med. **54**:524, 1927.

21. Hastings, A. B.; Murray, C. D., and Murray, H. A.: Certain Chemical Changes in the Blood After Pyloric Obstruction in Dogs, J. Biol. Chem. **46**:223, 1921.

two of our experiments increased, 100 and 300 per cent. Later analyses were always markedly higher, which shows that the formation or retention of nonprotein nitrogen is a late event in the picture. All the other symptoms are already well developed, which we believe is a point of importance.

In interpreting a rise in nonprotein nitrogen one must consider necrosis, blood concentration, scanty secretion of urine and kidney damage. For necrosis, we have been unable to find any evidence, either grossly or histologically. As a matter of fact, there may be a good deal of tissue degeneration and absorption without a rise in blood nonprotein nitrogen, as shown in Dragstedt's experiments.[15] Blood concentration would of itself increase the percentage of nonprotein nitrogen in the blood.

TABLE 3.—*Urine Excretion of Dog 13* with a Distended Thiry-Vella Fistula*

Date	Amount of Urine, Cc.	Daily Chloride Excretion Urine and Juice, Gm.	Nonprotein Nitrogen, Gm. per 100 Cc.	Total Daily Excretion, Gm.
10/11/30	420	2.81	1.62	6.8
10/12/30	370	2.35	1.62	6.0
10/13/30	325	2.04	1.90	6.1
Inflated				
10/14/30	460	3.82	1.62	7.4
10/15/30	330	3.71	1.68	5.5
10/16/30	470	3.19	2.10	9.9
10/17/30	465	2.55	1.50	7.0
10/18/30	245	1.32	2.14	5.2
10/19/30	195	1.07	1.53	3.0
10/20/30	160	0.85	1.86	2.9

* The dog weighed 15 Kg.; it died on Oct. 20, 1930.

The resulting viscosity and reduced rate of circulation might impair renal response. That this is not the important factor is, however, shown by two facts. First, that the increase in nonprotein nitrogen outruns the blood's concentration, and second, there is a normal amount of urine and an actual increased excretion of nonprotein nitrogen until the terminal stage appears. The evidence for kidney damage is thus slight during the larger part of the experiment. The evidence for this argument may be seen in tables 1 and 3.

Since the increased nonprotein content of the blood does not seem to be a simple kidney retention phenomenon there seems to be no other alternative except to assume there is an increased production, the exact cause of which we do not know.

Whatever the cause of the increase in nonprotein nitrogen may be, we do not believe it is the fundamental disturbance. The fact that it is a late event in the picture after all the other symptoms are well developed indicates that it is a result and not a cause.

Evidences of dehydration were present in nearly all of our animals. The usual decrease in blood and plasma volume may be seen in table 1, and this loss of water is reflected in the tissues, as may be seen in table 4. We had hoped to be able to separate the two factors, dehydration and dechlorination, but in only one animal has there been any evidence of such a possibility. Dog 50 was subjected to three periods of distention. In the first of these plasma volume decreased from 636 to 437 cc. and chlorides fell only from 495 to 412 mg. per hundred cubic centimeters at which time the period was terminated. In the second period plasma volume fell from 629 to 427 mg. and salt from 484 to 412 mg. In these two experiments the animal showed no symptoms. In the third period the plasma volume dropped from 621 to 406 mg., about the same

TABLE 4.—*Tissue Analyses for Chloride and Water*

	Biopsy		Necropsy	
	Water, per Cent	NaCl, Mg. per 100 Gm.	Water, per Cent	NaCl, Mg. per 100 Gm.
Dog 42				
Muscle	75.5	441	66.7	225
Skin	47.8	453	50.8	234
Intestine	71.2	686	72.2	225
Dog 43				
Muscle	71.2	410	72.9	374
Skin	64.8	508	57.3	477
Intestine	78.7	282	81.4	160
Dog 37				
Muscle	79.1	424	74.9	357
Skin	64.9	683	51.6	766
Dog 39				
Muscle	74.9	641	70.6	413
Skin	48.9	518	52.7	467

as before, but the salt was allowed to drop from 462 to 330 mg. At this time the animal showed all the symptoms of typical distention. The decrease in blood plasma being no greater in the third period, the result was naturally attributed to the low chloride content of the blood and tissues. Gamble and Ross [22] have also reported the loss of one dog in which there were no signs of loss of water but marked dechlorination. In view of the literature on edema, a decrease in chloride, no matter which ion is responsible for the effect, would ordinarily be associated with loss of water, and such we believe to be the usual case in the distention experiment.

Since vomiting was not sufficient to account for the loss of chloride in our animals, our attention was turned to the total loss in the urine and in the secretion from the fistula. In table 3, it may be seen that the total excretion of chloride at once increases on inflation of the loop.

22. Gamble, J. L., and Ross, S. G.: The Factors in the Dehydration Following Pyloric Obstruction, J. Clin. Investigation **1**:403, 1925.

The figures are minimal, due to the difficulty of getting all the secretion from the fistula from the cage and from the animal's body. Since the appetite fails almost immediately in an experiment as short as this one, the loss of chloride after the second day is almost entirely uncompensated. By the time of death the animal had therefore actually lost about 12 Gm. of chloride computed as sodium chloride. On the basis that normally he had about 2.5 Gm. chloride per kilogram of body weight, his loss would represent about one third of his total, quite enough to bring about serious disturbances in bodily functions.

There is no mechanism apparent by which distention might cause the kidney to increase its excretion of chloride, and, as a matter of fact, workers generally report a decreased excretion of salt in the urine in obstruction. The obvious pathway for loss of salt in our experiments

TABLE 5.—*Secretion of the Fistulous Loop*

Dog		Plasma NaCl, Mg. per 100 Cc.	Rate of Secretion per Hour, Cc.	NaCl Content of Juice, Mg. per 100 Cc.
50	Normal	610	1.0	759
	Distention	544	8.0	697
40	Normal	596	1.0	759
	Distention	502	21.8	759
46	Normal	643	3.0	693
	Distention	511	7.1	577
43	Normal	627	1.2	462
	Distention	561	13.2	693
54	Normal	627	1.4	759
	Distention (denervated)	610	17.0	792
55	Normal	627	4.2	676
	Distention (denervated)	627	23.0	792

is the secretion from the distended loop, and this we have carefully studied in many animals. In table 5 we have collected data for several of these on the rate of secretion and salt content before and during distention. The latter is also compared with the plasma chloride. During distention the high rate of secretion and its richness in chloride is most striking and leaves no doubt as to the real source of chlorine and water loss. In extreme cases such as dog 40, over 500 cc. of fluid may be secreted daily by a 15 cm. loop of the upper portion of the jejunum. The salt in this amount would be 3.9 Gm. This particular dog weighed 12.5 Kg. His total salt content was about 30 Gm. There was a total of 5.3 Gm. in his blood by actual determination. He therefore lost daily over 10 per cent of his total chloride and 74 per cent of his total blood chloride. It is obvious that life could not long continue without a greatly increased salt intake. Even with one of our two lowest rates of secretion, such as in dog 46, the loss of chloride amounts to 1 Gm. per day.

That distention is a powerful stimulus to intestinal secretion is seen from these figures. Lim, Ivy and McCarthy [23] have reported this mechanism for the stomach, but its part in intestinal obstruction, so far as we can find, has been overlooked. Increased hydrostatic pressure in obstruction has been generally regarded as due to an accumulation of the normal secretions, and it has been believed to lead to reabsorption rather than increased rate of secretion.

There are several reasons for thinking this output of intestinal juice is a true secretion and not a transudation because of pressure injury to the mucosa. It begins at once on the application of pressure. In dog 55 the determination of secretory rate immediately followed insertion of the balloon. It is for this reason that the two values for plasma chloride are the same. After five days of distention the increased secretion ceases within from four to six hours after removal of the balloon. Further evidence that the juice is not a transudate but a secretion is found in the fact that the chloride content of the juice is regularly higher than that of the plasma, and it may rise as the chloride content in the plasma falls. We have at present no explanation of this important fact. The juice at all times had the normal amount of invertase. This was determined by comparing the effect of juice from normal and distended loops on the hydrolysis of sucrose. The hydrolysis curves of the two juices were exactly similar. For all these reasons we regard the juice as essentially a true secretion.

As evidence that the losses of salt and water were of sufficient magnitude to be of real importance to the tissues, we have made analyses from biopsy and necropsy material. Skeletal muscle, skin and intestinal muscle all show losses in their salt content, sometimes as much as 50 per cent. The loss of water is greatest in the skin.

In animals that do not vomit, such as rabbits, a great collection of fluid is found in the contents of the distended intestine and stomach. This observation of Bunting and Jones [24] we have several times confirmed. In a rabbit weighing 2.4 Kg., 320 cc. of fluid was found in the stomach and duodenum. That this fluid came in part from the animal's blood volume was shown by 100 per cent increase in hemoglobin. The chloride content of the fluid amounted to 1.8 Gm., which was nearly a third of the total body chloride. These results indicate that the cause of death from obstruction in rabbits is essentially the same as that from distention in our dogs.

23. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. E.: Contributions to the Physiology of Gastric Secretion: I. Gastric Secretion by Local (Mechanical and Chemical) Stimulation, Quart. J. Exper. Physiol. **15**:13, 1925.

24. Bunting, H. C., and Jones, A. P.: Intestinal Obstruction in the Rabbit, J. Exper. Med. **17**:192, 1913: **18**:25, 1913.

If our contention is correct that dechlorination is the important factor in death from distention, it should be easy to test the matter by transfusions of sodium chloride. Although the literature is conflicting on this point, a number of workers have reported successful experiments after obstruction, among whom are Haden and Orr,[19] Jenkins [6] and Armour [8] and his co-workers. In our first attempt we transfused with 0.9 per cent sodium chloride whenever the hemoglobin showed increasing concentration. We hoped in this way to add salt and maintain blood volume. The dog endured distention eleven days in fairly good condition, which was evidence that the treatment was beneficial. After every injection there was, however, a marked increase in the amount of secretion from the fistula. It was evident that we were really defeating the purpose we had in mind, and that the blood volume and its chloride content were being subjected to continual fluctuations. Furthermore,

TABLE 6.—*Effect of Introducing 30 Cc. of 10 Per Cent Saline Daily into a Second Fistula During Distention of a Thiry Loop in Dog 40*

			Blood								Plasma	
Experiment No.	Procedure	Weight, Kg.	Hemoglobin, Gm.	Red Blood Cells, Millions	Volume, Cc.	Volume in per Cent of Weight	NaCl, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Alkali Reserve, Cc.	Volume, Cc.	NaCl, Mg. per 100 Cc.
1	Normal.....	13.44	11.8	7.60	1,180	8.7	478	29.7	46.2	661	610
	Distention.....	11.50	13.5	7.07	1,009	8.7	478	27.1	47.4	505	579
2	Normal.....	12.46	13.0	7.32	1,182	9.5	453	31.8	47.6	623	585
	Distention.....	12.10	13.8	8.37	1,217	10.0	429	34.2	51.6	596	594

this experiment did not clearly show that chloride was the therapeutic factor, since blood volume was also increased.

We therefore decided to administer 10 per cent saline directly into the intestine. To do this we prepared dog 40 with two fistulas, one a Thiry and the second a modified Thiry, connected distally to the jejunum. While the animal was undergoing distention, 30 cc. of salt was daily run into the second fistula. This dog endured two periods of distention of fourteen days each without symptoms of any kind. The fact that chloride without any significant amount of water maintained normal blood may be seen in table 6. As a control the dog was subjected to a third period of distention without the administration of salt. The disastrous effects during this period may be seen under experiment 50 in table 1.

A Nervous Factor.—It was early noted that at the moment of distending a loop the animal often showed signs of nausea. This was followed by a temporary disinclination for food. Although the appetite temporarily returned, by the fourth day, on the average, a permanent

anorexia developed. The uncompensated loss of chloride from the loop which now resulted has already been emphasized. The appetite which determined the intake of food thus became very important, for if the dog were only eating enough he could, of course, make up for his loss of chloride. Since the appetite failed before the chlorides in the blood had greatly decreased, we were led to suspect that it was inhibited by sensory nervous stimulation from the loop. This loss of appetite Burget [18a] has also noted if the pressure were allowed to rise in his closed intestinal loops.

It is obvious that if an inhibition of the appetite prevented a sufficient intake of chloride, any removal of the inhibition would be of benefit to the animal. We therefore decided to denervate a series of animals with Thiry loops. The arteries and veins of usual sized loops

TABLE 7.—*Effect of Distention of Denervated Thiry Fistulas*

			Blood							Plasma		
Experiment No.	Procedure	Weight, Kg.	Hemoglobin, Gm.	Red Blood Cells, Millions	Volume, Cc.	Volume in per Cent of Weight	NaCl, Mg. per 100 Cc.	Nonprotein Nitrogen, Mg. per 100 Cc.	Alkali Reserve, Cc.	Volume, Cc.	NaCl, Mg. per 100 Cc.	Plasma, per Cent
52	Normal	18.56	12.0	6.34	1,709	9.5	495	26.1	43.8	1,114	614	63.0
	Distention	17.50	10.8	6.20	1,354	7.7	519	30.0	43.8	853	645	63.0
54	Normal	13.28	12.5	7.04	1,200	9.0	495	29.7	43.9	706	627	58.9
	Distention	13.76	12.5	6.44	1,160	8.4	486	31.5	42.4	603	610	52.0
60	Normal	17.56	10.2	6.29	1,718	9.8	495	29.4	48.1	1,082	627	63.0
	Distention	18.56	14.0	8.56	2,035	10.9	478	28.5	49.2	1,038	610	51.0

were dissected entirely free of all surrounding tissue, the nerve strands being picked up and a wide segment removed to prevent regeneration. The artery and vein were then painted with full strength phenol, which was removed with alcohol and saline. The pedicle of the loop then consisted of nothing but the afferent and efferent vessels. We now have experiments on eight animals prepared in this way. Three of these endured distention twenty, twenty-one and twenty-three days without any symptoms, at which time the experiments were discontinued. The blood of each remained normal except for a shrinkage of volume in no. 52. The data from these three dogs are shown in table 7.

Two dogs were without symptoms for a week, when the experiments were terminated, in one case by distemper and in the other by an actual obstruction and rupture due to adhesions. One dog was without symptoms or blood changes for thirteen days, at which time an accidental rupture of the loop occurred. A seventh animal was without symptoms for eleven days, and then quit eating. There were no other symptoms, but the blood had definitely changed toward the obstructed

type. The eighth dog showed no protection whatever, which we hope was due to a failure in denervation. Of these eight dogs, three showed complete immunity to distention and four others undoubted protection. All these animals showed high secretory rates on distention; the two latter animals, however, had the highest rates we have ever observed, 30 cc. per hour in one and 23 cc. in the other. We believe the high loss of salt in these cases was more than could be compensated for by a normal appetite and intake of food. Sooner or later the usual symptoms had to appear.

A study of these denervated animals has convinced us that anorexia due to stimulation from the distended loop is one of the fundamental factors in the development of dechlorination. In distention not only is chloride lost by an increased loop secretion, but the intake is also curtailed. Both the eating of salt and the administration of it, either by vein or by fistula, become devices for maintaining the body chloride.

COMMENT

The introduction of isolated intestinal loops by Whipple and his co-workers [25] was the first important advance that has been made in the study of intestinal obstruction by experimental methods. Outstanding as this procedure was, it still did not allow the various factors concerned in obstruction to be dissociated from each other. We believe that our method of distending open fistulous loops accomplishes this necessary condition, and that for the the first time, some of the factors can be studied independently.

From the data presented, it is evident that distention of an isolated intestinal loop produces a train of symptoms identical with those observed in acute high obstruction, and since obstruction is regularly accompanied by distention, the symptoms in all probability have a common origin in the two conditions. Our studies then have made it possible to follow the sequence of events both in distention and obstruction.

There is no evidence of toxemia either from bacterial invasion or necrosis of intestinal tissue. On the application of pressure the animals at once usually show some signs of restlessness and nausea, and vomiting may occasionally occur. These reactions are temporary and usually disappear within a few hours. The first permanent symptom to attract attention is a marked increase in the fluid flowing from the loop. This seems to be a true secretion resulting from the mechanical stimulation of the loop, since it contains ferments common to those in succus enteri-

25. Stone, H. B.; Bernhaim, B. M., and Whipple, G. H.: Intestinal Obstruction: A Study of the Toxic Factors, Bull. Johns Hopkins Hosp. **23**:159, 1912.

cus. It is extremely rich in chloride, the daily excretion often being in excess of the animal's normal intake. Although after the initial period, obvious gastro-intestinal reflexes may be lacking, the animal is receiving sensory stimuli from the loop. Whether these are conscious or subconscious can, of course, not be told. There are no signs of pain but rather an appearance of general malaise. The appetite slowly fails, and by the fourth or fifth day, complete anorexia supervenes. A nervous factor once suggested but long since denied is thus seen to be of importance. The output from the loop, amounting to several hundred cubic centimeters per day, is now entirely uncompensated so far as chloride is concerned. Although the animal may still take water, it does not equal the amount lost through the secretions, respiration and insensible perspiration. Both plasma and total blood volume now show decreases. The plasma chloride content falls daily. The hemoglobin and nonprotein nitrogen rise. The tissues appear desiccated, and both desiccation and dechlorination are borne out by chemical analyses. Of these two factors the dechlorination seems to be the more important. By the time the plasma chloride has decreased 25 per cent on the average, the animal is in coma and death imminent. Since the decrease of chloride in the blood and tissues is the one finding absolutely constant, and since restoration of blood chloride brings relief, it is believed to be the most important factor in causing death from experimental distention and acute high intestinal obstruction. Death in all probability is due to changes in the electrolytic condition of the cells so marked that life itself is made impossible. Distention of an intestinal segment may be the initiating cause of the whole train of symptoms.

The authors are not in a position to make any extended comparison of their experimental procedures with clinical conditions, and only a few remarks need be made on this point. In acute uncomplicated obstructions there is distention and loss of fluid and chloride into the bowel. In animals the amount lost in this way is enough to lower the body fluids and chlorides below the danger point, and there is no reason for doubting that this occurs in human cases. Since distention is in itself responsible for such a serious sequence of events, it is obvious that the reduction of the distending pressure above an obstruction is to be considered. Maintenance of body fluids and their salt content must also be important therapeutic measures.

Although the term "dechlorination" has been used throughout this paper, it is possible that the term "demineralization" would be more appropriate. While the evidence for a disturbance in the body chloride seems convincing, other eletrolytes may also be concerned. So far no distinction has been made among the various chlorides. In addition, the loss of the cation of these salts must not be overlooked.

SUMMARY

1. By the distention of Thiry and Thiry-Vella fistulous loops of the upper portion of the jejunum all the symptoms of acute high intestinal obstruction may be reproduced. The advantage of this method lies in the avoidance of immediate operative effects and in the possibility it gives of isolating certain of the factors involved.

2. Constant distention of the loops with from 50 to 80 mm. of mercury results in malaise, loss of appetite, excessive secretion from the loops, desiccation and dechlorination of tissues, decreased blood and plasma volumes, increased hemoglobin content, moderately increased alkali reserve, high nonprotein nitrogen and greatly decreased blood chloride. Death occurs on about the eighth day.

3. The evidence that death is not due to a toxemia seems conclusive. Drainage of all fluid from the loop exteriorly does not prevent a fatal outcome, but drainage back into the continuous intestine prevents symptoms from appearing. This precludes toxemia either from bacterial products or necrotic substances from the intestinal wall. Denervated loops also withstand pressure, often with entire impunity.

4. Death is believed to be due primarily to the loss of chloride which is poured out by the loop under the stimulation of the mechanical pressure. This is almost invariably accompanied by decreased blood and plasma volume, but that the loss of chloride is the more important factor is evidenced by the fact that animals may be kept alive by introducing small quantities of 10 per cent salt directly into the intestine.

5. A nervous factor has been demonstrated in the train of symptoms. Dogs with denervated loops may withstand pressure indefinitely. They do not lose their appetites and thus maintain their body chlorides, even in the face of an exaggerated loss through the distended loop.

Book Reviews

Special Cytology. Edited by E. V. Cowdry. Second edition. In three volumes. Price, $30. Pp. 1,839, with 757 illustrations. New York: Paul B. Hoeber, Inc., 1932.

The "Special Cytology" has, after four years, appeared in a second and augmented edition; this new edition has been extended to include three volumes, whereas the first was confined to two; there are numerous additional illustrations, five hundred more pages (now totaling over eighteen hundred) and nine new sections. Twenty-seven of the entire forty-four chapters have received little or no modification; seven have been considerably altered. To produce this work, the assistance of forty-six contributors was sought—in itself an editorial task of imposing proportions; by it the English reader is brought handily to sources the separate collection of which would be an overwhelming labor.

Each section conveniently carries its own table of contents and ends with a list of references, frequently imposing in length and abundant in selected items; there is a total of almost two thousand in the first volume alone.

Many of the works cited were written within the last decade; yet there is more than a little truth in an introductory statement that modern cytology shows a gratifying tendency to revert to the earlier scheme of studying living cells (by microdissection and by examination of translucent tissue). In the present work there are reported original investigations on the physical consistency and the finer structure of the cells in untreated skin — their intercommunicating protoplasmic fibrils and granular mitochondrial elements. Other recent studies on the skin are reported, which stress its importance as a manufactory for enzymes, hormones and antirachitic and immune bodies and its office as a whole membrane through which chemical substances pass en route to the circulation. Modern histology thus turns back to a study of layers — of major interest a century ago.

One is reminded that the nasal secretion was for ages considered an excrementitious humor distilled within the cerebral ventricles and passed into the nose and mouth through a cribrose nasal roof. The true source of this functionally important secretion — the mucous membrane — is fully described, and the cellular features contributory to its striking activity are carefully reviewed. The discussion is not extended, however, to include the buccal or labial mucous membrane, which latter is still incorrectly described in textbooks despite the fact that Frederic Ruysch, as early as 1703, presented an admirable account of its peculiarities.

The histology of the lower respiratory tract is described, and the nature of the alveolar epithelium is displayed by original preparations. In the excellent chapters on the cytology of the alimentary tract and its glandular outgrowths, one finds a most serviceable group of figures, nearly one hundred in number, which display the various intracellular mechanisms, their elaborated products and the paths within the cell traversed by the latter; however, as the reader is cautioned, the time has not yet come when the investigator may with certainty state which substances within the active cells produce the physiologically recognized secretion; nor can a specific enzyme be discovered infallibly by a given microchemical method.

About two hundred years ago a Fellow of the Royal College of Physicians in London recorded his perplexity regarding the functions of the spleen. He put aside unequivocally the "variety of schemes" laid down from ancient times, and, finding, through extirpation in animals, that the organ was "unnecessary to individuals," he believed that it must be designed for some office in promoting the propagation of the species, since organs are not by nature contrived in vain! The contributor to the current work must still admit that "little is known concerning

the functions of the spleen," functional interpretation being inherently difficult whenever an organ's parenchymatous parts are not peculiar to it. A clear account, however, of histology of the spleen can be and is presented, and its relation to hematopoiesis is discussed. Five excellent sections follow on the formed elements of the blood; but, of the containing vessels, only the capillaries receive attention—and these in a closely written, lucid account. The endocrine glands are dealt with in four sections; the section on the pineal body is new, and replaces an earlier and much longer section which contained a great deal of interest in comparative anatomy and histology; the section on the suprarenal is almost wholly physiologic. The section describing the renal tubules makes clear not only the regional cytologic differences, but the comparative embryologic basis of these. To cartilage less space is given than some textbooks allot to this important subject, and one which is the object of increasing clinical inquiry. Admitting that in an edited work, all chapters cannot be of equal value, it still seems that this account falls rather too far short of the standard set by certain European works of similar type. Synovial membranes are allotted a section; fortunately, one must admit, since the author states that there still exists the opinion "that joints and bursae are lined by endothelium." The several kinds of muscle are discussed, and the specialized systems of the heart are described in a convincing anatomic account which brings one again near the dependable older sources and points out recent errors in description.

The original chapter on the eye has been extended to include the choroid, the sclera and the pathologic changes in all the layers. The collection of figures of the visual elements in various vertebrates is unique and most valuable. The degree to which this and several other excellent chapters have been changed seems to be a measure of the individual author's painstaking effort to render his section not only a more inclusive account, but also a more accurate appraisal of the numerous investigations, rather than being "a rough measure of activity in the lines of research represented." A very good new chapter has been added descriptive of the cornea and the lens.

The internal ear, nerve cells, neuroglial elements and cerebrospinal pathway are discussed and a section on microdissection of the nerve cells has been added. The cytology of the uterine gland cells; the ovary, ovum and tubes; the cells in the vaginal fluid and the mammary gland are discussed by those who have contributed greatly to recent knowledge of these elements. The interstitial cells of the testis, the germ cells and the cytology of the seminal vesicles, prostate and bulbo-urethral glands are the closing subjects—all ably handled.

In general, it may be said that many of the cytologic figures suffer in not being reproduced in their original colors to display effectively the significant cellular tinctorial materials. There are few omissions, and doubtless they were purposeful and well considered; one may note the following: connective tissue proper; tendons; arteries, veins and lymphatics; the mucous membrane of the mouth, the lips, and the large and small intestines; serous membranes; the non-nervous labyrinthine epithelium; the lymph glands; the nails. It seems curious indeed that in such an extensive and modern work on cells, prepared almost three hundred years after Hooke first commented on cell-shape, no mention is made of the three-dimensional form of these fundamental units of bodily structure; yet the superb recent studies of cellular morphology, published by an American anatomist, are readily available to the editor.

Many of the contributors succeed in their attempt to integrate structure, normal function and deranged activity of the cells and the organs, and so not only provide informative and provocative narratives, but broaden the usefulness of the volumes. Many readers will not agree, however, that, without the inclusion of physiologic and pathologic discussion, the presentation would be "both sterile and uninteresting."

Internal Medicine: Its Theory and Practice in Contributions by American Authors. Edited by John H. Musser, B.S., M.D., F.A.C.P., Professor of Medicine in Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Price, $10. Pp. 1316, with 16 tables and 39 illustrations. Philadelphia: Lea & Febiger, 1932.

Whenever a textbook of medicine is published in this country, it is the natural instinct for many to contrast the new book with Osler's "Practice of Medicine." The appearance of Dr. Musser's volume compares not unfavorably with such a model. The first edition of Osler's work, which was published forty years ago, contained 1,050 pages of text, each page averaging around 500 words. The first edition of this new book contains 1,293 pages of text, each page averaging, also, around 500 words. The type is clear and easy to read; the paper is of good quality, so that the pages turn over comfortably; the book weighs only about 5 ounces more than its eminent predecessor, and it can be handled just as easily, is attractive looking and is of convenient shape and size. So much for the book's physical characteristics.

The new "Internal Medicine" is a textbook on theory and practice, covering the entire field of medicine. It is written by a group of twenty-seven well known American authors and is edited by one of them. The editor has been remarkably skilful in smoothing out the individual peculiarities of literary style among his contributors so that the reader is not irritated by abrupt changes in methods of presentation or expression on the different subjects discussed. The editor, too, has balanced the contents of his book most carefully, giving due space to subjects of general clinical interest and curbing the verbosity of his co-workers who have written about rare diseases. Thus, the importance of no single subject is overemphasized or minimized.

Since each contributor is a teacher, thoroughly familiar with the ground he covers and well trained in the art of presenting medical facts in an interesting fashion, the entire book makes good reading. Some of the sections are necessarily very short; on the other hand, no space is wasted by useless charts, diagrams or words. The information put forth is expressed in concise, up-to-date English, and the various methods of diagnosis and treatment that are advocated are sound and of established value.

The description of many diseases begins with a short historical narrative mentioning the important names and publications to be remembered as best recording the development of knowledge in regard to the subject under consideration, and each section ends with a few references to direct those interested into the way of more comprehensive reading. A good index completes the book.

On the whole, this new textbook is admirable. Teachers, students and practitioners will enjoy it, not only because it is well and clearly written, but also because it opens up the vast field of medical knowledge in a simple, interesting and engaging manner.

Klinische elektrokardiographie, mit einem Grundriss der Arhythmien. Von Dr. Wilhelm Dressler, Assistent der Herzstation in Wien. Mit einem Geleitwort von Prof. Dr. C. J. Rothberger. Second improved edition. Paper. Price, 12 marks. Pp. 148, with 118 illustrations. Berlin: Urban & Schwarzenberg, 1932.

In the preface to this work, Professor Rothberger expresses the belief that Dr. Dressler has met the requirements for introducing clinical electrocardiography to the practitioner of medicine. This belief is amply justified by the work. It is accurate, succinct, clear and a model of simplicity. It deals mainly with proved facts and touches only lightly that speculative field that brings confusion to all except the advanced student.

The first three chapters deal with the principles of the galvanometer, with the instrument itself and with the normal electrocardiogram. Following this is a

discussion of the alterations produced by malposition and by hypertrophy of the heart. Against this portion of the book a just criticism may be advanced. The author states, without qualification, that right or left ventricular hypertrophy may be determined from the electrocardiogram. Many observers believe that muscle mass and electrical activity are frequently but not always associated. It is probable that many normal hearts will show the curve of right or left ventricular preponderance.

The fifth chapter, which occupies the major portion of the book, has to do with the disorders of the heart beat. These are divided into two groups: disorders of stimulus production and those of stimulus conduction. In the first group are found sinus tachycardia and bradycardia, sinus arrhythmia, escaped beats, nodal rhythm, extrasystoles (auricular, nodal and ventricular), paroxysmal tachycardia (auricular, nodal and ventricular), parasystole, flutter and fibrillation. In the second group one finds auriculoventricular block, sino-auricular block, bundle branch block and arborization block.

The sixth and concluding chapter is a brief one which discusses the curves that indicate probable myocardial damage and coronary disease.

An especially pleasing feature of the book is the excellent summary that follows each group of tracings and sets forth the clinical recognition, the significance, the prognostic value and the therapeutic indications for the particular group.

Because of its simplicity and clarity, the book recommends itself equally to the undergraduate student and to the practitioner.

The Chemistry of Tuberculosis. By H. Gideon Wells and Esmond R. Long. Second edition. Cloth. Price, $7. Pp. 500. Baltimore: Williams & Wilkins Company, 1932.

It may seem paradoxical that in a disease process seemingly so well defined and meticulously studied through these many decades as tuberculosis, a review such as that of Wells and Long would present a picture of absolute fluidity, of constantly changing views.

While paradoxical, it is nevertheless extremely hopeful. The tremendous activity in tuberculosis research which necessitates such constant revision is particularly apparent when one compares the second with the first edition of the review under consideration, and we may take considerable pride in the fact that American investigators have themselves contributed much to the newer information that is summarized in the book of Wells and Long.

Particularly the first chapters have been subjected to thorough revision so that they present a most complete review of the knowledge that has developed. There is no material expansion in the length of this portion of the book, because obsolete material has been largely eliminated. Some of the chapters have been practically rewritten, as, for instance, those on the chemistry of the tubercle bacillus and on the specific products of the tubercle bacillus. As a matter of fact, Long himself has contributed in a large measure to the advance that can here be recorded.

The material that deals with the chemical make-up of the patient has perhaps required less treatment. It is interesting to note the conservative tone in the discussion of chemotherapeusis. As one specific after another has been discarded, investigators have become more and more skeptical until today other paths, some of them older, are being assiduously retraced. Ultimately, too, we shall probably place much less reliance on the guinea-pig and study the patient more closely.

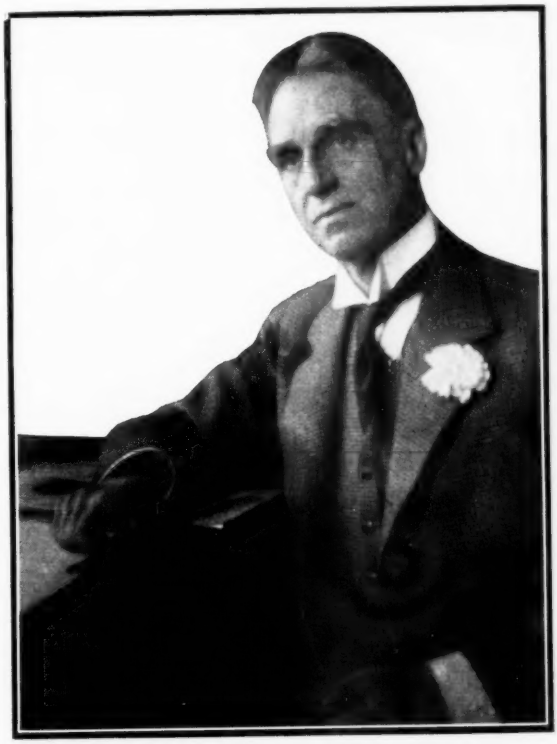
The first edition, from the time of its publication, has been on the desk of every tuberculosis worker. It filled a distinct need in making available in short, concise form a review of almost everything that had to be known about the chemistry of tuberculosis. The new edition will therefore be welcomed, as it is not only complete and clear, but accurate and fair in its evaluation of investigative work dealing with the tuberculosis problem.

Dr. Lydia DeWitt shared in the preparation of the first edition. As a result of her death, the revision of the third section has been in the hands of the two senior authors and all the newer methods of treatment have been reviewed by them.

AN APPRECIATION

Dr. Thayer was a member of the first Editorial Board of the ARCHIVES OF INTERNAL MEDICINE and continued to serve in this capacity for twenty-four years.

His fine ideals and broad scholarship made him an invaluable member, and he played an important part in the endeavor to establish and maintain high standards. He never lost sight of the purpose for which the ARCHIVES was established, namely, to further clinical investigation by supplying a medium of publication.



WILLIAM SYDNEY THAYER, M.D.

In passing on manuscripts, he always bore in mind both the writer and the prospective reader. If a paper was not quite up to standard but showed evidence of industry and ideals, he would in his kindly manner suggest to the author certain modifications which would make the manuscript acceptable. His kindliness to young physicians who showed promise of future attainments was unbounded.

In Dr. Thayer's death, American medicine has lost one of its most cultured and scholarly members.

J. L. M.